DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY COMMITTEE MEETING

Wednesday, September 15, 2004

8:10 a.m.

ACS Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

P. Joan Chesney, M.D. C.M., Chair
Jan N. Johannessen, Ph.D., Executive Secretary

Deborah L. Dokken, M.P.A.
Steve Ebert, Pharm.D.
Michael E. Fant, M.D., Ph.D.
Samuel Maldonado, M.D.
Robert M. Nelson, M.D., Ph.D.
Thomas B. Newman, M.D., M.P.H.
Judith R. O'Fallon, Ph.D.

FDA Participants

Solomon Iyasu, M.D.
Dianne Murphy, M.D.

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P R O C E E D I N G S

DR. CHESNEY: Good morning. I think we're ready to begin today's deliberations, and I'd like to say that we're not going to introduce the committee members until Dr. Murphy has given us an overview of the previous and current committees. And so we really just, I think, need to start off the meeting by having Dr. Johannessen read the meeting statement.

DR. JOHANNESSEN: Thank you, and good morning. The following announcement addresses the issue of conflict of interest with regard to the study drug, dextroamphetamine, and competing products used for the treatment of ADHD and to the adverse event reporting session and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential for an

appearance of a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants:

Dr. Patricia Joan Chesney for ownership of stock in a company with a product at issue valued at between $25,001 and $50,000, and for her spouse's honoraria for speaking on unrelated topics at a firm with a product at issue valued at less than $5,000;

And Dr. Robert Nelson for an honorarium for speaking on an unrelated topic at a firm with a product at issue valued at less than $5,000.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. In the event that the discussions involve any other firms or products not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such

involvement, and their exclusion will be noted for the record.

We would also like to note that Dr. Samuel Maldonado has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Maldonado is employed by Johnson & Johnson.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement in any firm whose product they may wish to comment upon.

Thank you, and we'll now turn it over to Dr. Dianne Murphy.

DR. MURPHY: I wanted to just take a moment to welcome everybody and to also tell the committee that you may not have realized--or a number of people on this committee, that you have just made a transition. That transition has been from a subcommittee, which was providing very important advice to us, but to now a full committee, which advises the Commissioner directly.

And you have certain responsibilities that are slightly different, and I'm going to go over those in a second. And also to the fact that you are not only just a full committee advising the Commissioner, but that, as I said, you have certain responsibilities that you're going to hear some of them today that are clearly defined.

You have moved from the Center for Drugs to the Office of the Commissioner, and the office has been--and this committee is now administered there the Office of Science. And our new Exec. SEC. is Jan Johannessen, who has done an extraordinary making sure that everybody has been recruited and met all the criteria that we need to meet and getting you here and assembled and in helping us charter this new committee.

It is really just a monumental feat because the agency basically was not allowed to have any new committees. It actually took Congress to create you. So I'm spending a little time on this so you'll understand how important your deliberations are to the agency.

One of the other activities that has occurred, as you know, is that there has been the creation of the Office of Pediatric Therapeutics, and that office is now responsible for all pediatric activities across the agency. And, therefore, this committee may be hearing more--having been in the Center for Drugs previously, you may be hearing more about other products such as devices or formula. So I wanted to make sure that you are also aware of that.

And I know sometimes that's a bit overwhelming if you're a cardiologist or an ID doc or whatever your training. The breadth of what we're asking you to deliberate upon is quite large. However, as those of you who have been on the previous subcommittee are aware, we always bring in additional experts, that you're here to bring particularly to those deliberations the pediatric perspective, because we have lots of technical committees that have lots of expertise, and we will always bring that additional expertise as needed to the deliberations. But it's your particular

pediatric perspective and expertise that we depend upon at these meetings.

I did want to spend a moment introducing, so that you can put some faces with names, the people who are now in the Office of Pediatric Therapeutics, which is Sara Goldkind, who will be speaking; Solomon Iyasu, whom you know, who has been on detail with us for a while; Ann Myers, if you'd put your hand up, Ann, who is our policy analyst, so you'll have a face there; and Jean Harkins, who is not here, but she is the person who actually runs the Office of Pediatric Therapeutics.

I mention that because it is that office that is mandated to particularly focus on the ethical issues and the safety issues, and that this committee within the Office of the Commissioner has now also been identified to deal with those issues.

I also wanted to comment on some other transitions for those of you who have been on the subcommittee. I'm no longer with the Office of Counterterrorism, Pediatric Drug Development. Rosemary Roberts is the new office director, and so

she's still going to be very active in the pediatric issues, and the Division Director for Pediatrics, Shirley Murphy, is now the Deputy within that office. And we have a new Division Director, just so you'll know these names. Lisa Mathis I do not believe is here. She's dealing with other issues this morning.

For the new members--and I apologize to the old members because I know you've heard this. I actually took it out of the slide on Monday because I didn't think that everybody really wanted to hear about all the accomplishments of the previous committee. But I wanted the new members to hear a little bit about what the previous committee has actually--some of the issues they have dealt with. And they have dealt with not only the ethical issues that have to do with normal volunteers, placebo-controlled trials, the vulnerable population within pediatrics. They have dealt with an enormous array of scientific issues, from sleep disorders, hepatitis C, HIV, antiviral drug development in neonates, the current

epidemiology and therapeutics and development of therapies for hyperbilirubinemia, clinical risk management for HPA axis suppression in children with atopic dermatitis, tracking cancer risks among children with atopic dermatitis, and as you all are aware, last February a discussion of the FDA process and review of therapies for major depressive disorder.

In addition, this committee has now reviewed--before today's additional eight products that you're going to be hearing about, has reviewed over 22 products that were granted exclusivity, and you have looked at the one-year post-adverse event reporting that has occurred for those products. I can tell you that this is an important process that we are looking to evolve constantly. It came up recently at a congressional hearing as to how were we doing this and what were we doing with it. And I think it's important that this committee realize that it is important what you have to say to us about whether we should do anything else in trying to follow--gain a better understanding of what

happens to children after these products have been either approved--or approved and particularly after they have been studied, because as you heard yesterday, they don't always get an approval or a label change, but certainly they have been studied and they may be granted exclusivity. And that in itself often results in additional information.

As you go around this morning, it would be helpful if you would identify if you were on the previous subcommittee. I'd appreciate that just so the new members will know. And also, I wanted to particularly thank Sam--and is Steve here? I don't see him. Oh, there you are. As Jan said, for doing double duty. We are still in the process of identifying the industry and consumer representatives, a total different process, and they very kindly agreed to continue to assist us in these last rigorous days, the last few days.

And, again, thank you for being here, for your participation, because I know it requires quite a commitment, and for your thoughtfulness as we move forward with this new committee.

DR. CHESNEY: Thank you very much, Dianne.

So I think we would like next to go around the room and have the new Pediatric Advisory Committee members introduce themselves, and I'd like to start with the members who are no longer on the committee, if they could--that was a joke. So let's start with Dr. Maldonado.

DR. MALDONADO: Sam Maldonado. I work in pediatric drug development at Johnson & Johnson, and as Dr. Murphy said, this is my last session with the committee. There will be a new member from industry.

DR. NEWMAN: I'm Tom Newman. I'm a professor of epidemiology and biostatistics in pediatrics at the University of California, San Francisco, and a general pediatrician, and I'm new to the committee.

MS. DOKKEN: I'm Deborah Dokken, and I am also new to the committee, and I am a patient-family representative and I really appreciate having that voice on the committee.

DR. O'FALLON: Judith O'Fallon. I'm a

professor emeritus of statistics at Mayo Clinic. I got called back half-time to cover a maternity leave, by the way, going back. But I've been on the committee since its beginning.

DR. FANT: My name is Michael Fant. I'm an associate professor of pediatrics at the University of Texas in Houston. My expertise is in neonatology and in biochemistry. And I'm new to the committee.

DR. NELSON: I'm Robert Nelson. I'm associate professor of anesthesia and pediatrics at Children's Hospital of Philadelphia and University of Pennsylvania. My clinical area is pediatric critical care, and I also work in the area of ethics, and I was on the previous subcommittee.

DR. EBERT: Hi, I'm Steve Ebert. I'm an infectious diseases pharmacist at Meriter Hospital and professor of pharmacy at the University of Wisconsin, Madison. I'm an outgoing member of the committee.

DR. CHESNEY: And my name is Joan Chesney. I'm a professor of pediatrics at the University of

Tennessee in Memphis, and my interest is infectious diseases, and I'm a former subcommittee member.

DR. JOHANNESSEN: My name is Jan Johannessen, and I'm the Executive Secretary to the Pediatric Advisory Committee.

DR. MURPHY: Dianne Murphy, Office Director, Office of Pediatric Therapeutics, FDA.

DR. IYASU: I'm Solomon Iyasu. I'm medical team leader with the Division of Pediatric Drug Development and an epidemiologist with the Office of Pediatric Therapeutics.

DR. CHESNEY: Thank you and welcome to all the new committee members. You're in for quite a ride, believe me.

Our first speaker this morning--and, again, for the new committee members, what you're going to hear about next was really a historic process and a historic meeting on Friday. And Dr. Sara Goldkind is going to introduce the topic for us. She's a board-certified internist who did a clinical fellowship in medical ethics at the University of South Florida. She also has a

master's degree in religious studies with a focus on comprehensive religious ethics--comparative religious ethics, excuse me, and she's been with the agency for almost a year, which she tells me seems like longer than that.

Dr. Goldkind?

DR. GOLDKIND: It's my pleasure to be here today at the inaugural meeting of the Pediatric Advisory Committee and to tell you about the work of the Pediatric Ethics Subcommittee.

As Dianne mentioned, this is really a landmark time in pediatric research. That's the way we see it because we feel that this committee as well as the Pediatric Ethics Subcommittee can really make incredibly important decisions and consensus statements regarding pediatric research.

So what I'd like to do now is talk a little bit about the role of the Pediatric Ethics Subcommittee. It is going to be a subcommittee that addresses Subpart D referrals and also ethical issues that impact on research affecting the pediatric population.

Going back to the part on Subpart D, there's a mistake in the slide, and where it says "Joint 21 CFR 50.54 and 45 CFR 46.407 referrals," those are referrals that will come to both OHRP and the FDA, and we actually had one of those to review on September 10th, which involved the effects of a single dose of dextroamphetamine in attention deficit hyperactivity disorder, a functional magnetic resonance study. And Dr. Nelson, who is the Chair of the Pediatric Ethics Subcommittee, is going to give you a summary of the deliberations of the Pediatric Ethics Subcommittee in that regard.

The subcommittee can also address referrals that come only to the FDA under 21 CFR 50.54, and I'm going to talk about these regulations in a little bit more detail. But if there are no referrals and there are burning ethical issues that we would like to address, we can also take those to the Pediatric Ethics Subcommittee for deliberation.

So now to go into a little bit more detail about the regulations under which we can have these

referrals, Subpart D is entitled "Additional Safeguards for Children in Clinical Investigations and Research," and they are essentially identical for DHHS and FDA. DHHS regs are Title 45, CFR 46, also known as "the common rule" because 17 federal agencies operate under those regulations. And the FDA regulations are 21 CFR 50.

There is a notable distinction between the two sets of regulations, and that is the issue of waiving parental permission can be done under Title 45, CFR 46, but not under the FDA regulations. But in terms of the Subpart D referral process and the general categories of pediatric research, those are identical between the two regulations. And what I've done in these slides is include the citations for both regulations.

So Subpart D has four different categories under which pediatric research can be conducted. The first category is 50.51/46.404, and that is a category which states that the research involves no more than minimal risk. And it essentially does not discuss who benefits from the research, but

basically describes that there's a ceiling of minimal risk for exposure for the children.

50.52/46.405 is research that involves greater than minimal risk but presents the prospect of direct benefit.

And then 50.53/46.406 involves greater than minimal risk but presents a prospect of generalizable knowledge about the disorder or condition, but there's no prospect of direct benefit to the participants.

So those are three categories under which an IRB can classify pediatric research. If the IRB determines that it cannot classify the research under those first three categories, however, the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and the FDA Commissioner or Secretary, after consultation with a panel of experts in pertinent disciplines, and following an opportunity for public review and comment determines the

following...

So, in other words, if the IRB feels that the research has merit for the general pediatric population but cannot be classified under one of the first three categories, it can make a referral to one of the federal agencies--and I'll discuss those details in a minute--to have the protocol reviewed by an expert panel.

And so what must the research then satisfy, according to the expert panel? The research, in fact, satisfies one of the first three categories, so the expert panel can make a determination that after it reviews the research, actually one of the first three categories does apply, or the following three conditions are met: the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; the research will be conducted in accordance with sound ethical principles; and adequate provisions are made for soliciting assent and parental permission.

The composition of the Pediatric Ethics Subcommittee is the following: Dr. Nelson is the Chair. According to FACA, we also need to have two members of the Pediatric Advisory Committee represented on the Pediatric Ethics Subcommittee. And in addition to Dr. Nelson, we included Dr. Chesney and Dr. Gorman. And we supplemented the Pediatric Ethics Subcommittee with an additional group of core ethicists: Drs. Fost, Kodish and Marshall.

The composition of the Pediatric Ethics Subcommittee under both DHHS regulations and FDA regulations states that the panel of experts in pertinent disciplines, for example, science, medicine, education, ethics, and law, and we selected from among those groups according to the protocol. But most of those groups were represented on the Pediatric Ethics Subcommittee that took place on September 10th. In addition, we also had two patient advocates represent on that subcommittee.

So once the IRB makes the determination

that it wants to refer to a federal agency, it refers to the FDA for regulated--if the products in the protocol are FDA-regulated, and it refers to OHRP if the research is federally funded or conducted. And we have a very close working relationship with OHRP, and when a protocol comes to us, we also refer it to them for review, and they refer a protocol that comes to them to us. And in this case, the protocol was actually submitted to OHRP, but upon our review it was noted that two of the products in the protocol, both the MRI machine and the dextroamphetamine, were FDA-regulated and so we also had jurisdiction over that protocol.

The review would then be conducted by the Pediatric Ethics Subcommittee expert panel, and as I said, each protocol--we will have a core group of ethicists, and it will be supplemented by appropriate expert panel members and patient representatives and/or community representatives.

The Pediatric Ethics Subcommittee will bring its recommendations to the Pediatric Advisory

Committee for endorsement, as Dr. Nelson will do today, and then those recommendations will be submitted to the Commissioner of the FDA for final determination. Once that determination is rendered, it will be forwarded to OHRP, and OHRP will send the Commissioner's memorandum on the Pediatric Ethics Subcommittee/Pediatric Advisory Committee's recommendations on to the Secretary, and the Secretary will have his final determination, particularly in regards to funding of the research.

So our goals in this process, clearly the overarching goal is to advance an understanding of pediatric research, and we'd like to do that involving additional expert input and public input. We also want to have transparency in the process, and in that regard we had an open public comment period before the Pediatric Ethics Subcommittee. We also had an open hearing available at the Pediatric Ethics Subcommittee. We also want to try and respond to these protocol referrals in a timely manner so that they will be helpful to the IRBs

involved. And we want to be able to handle these referrals in a consistent and clear manner so that they can advance the general understanding of pediatric research. And we would like to do this and are doing this in harmony with OHRP so that we have a united federal agency response to pediatric research.

Thank you.

DR. CHESNEY: Thank you very much.

Maybe what we could do is introduce and hear our next speaker and then ask for questions from the panel. Dr. Skip Nelson is the Chair of the Pediatric Ethics Subcommittee, and he will discuss with us the deliberations of the Pediatric Ethics Subcommittee with the invited folk that Dr. Goldkind just mentioned on last Friday. And the issue here is that Dr. Nelson has prepared a summary of the committee's deliberations, which you have in front of you, and I'll let him highlight issues that he wants to bring to your attention. And what we're looking for here is an endorsement by the committee. As we've mentioned, this took a

whole day of fairly intense deliberations last Friday, and we don't anticipate that we will have to repeat that process here. So we're just looking for the committee's endorsement and any questions that you may have, either for the process as Dr. Goldkind just outlined it or for the specific events of Friday as Dr. Nelson will present them.

DR. NELSON: Thanks. You have the document before you. Let me just note, as someone pointed out, I've got the wrong date in the heading. That will be corrected before the final version goes up. If you see any other typos, feel free to write them down and share them with us after our discussion.

I'd like to walk you through the document. My intent here is not to read the document but to highlight what is in it, since you can probably read faster than I can talk. The introduction simply restates the purpose of the meeting and then gives a brief summary of what's in the summary.

But let me first start with what is the primary issue that would be raised by this

protocol, which is the particular risk of the procedures that are contained within the protocol.

Now, as a preface to this, one of the first things that an IRB must determine--and for this exercise, the Pediatric Ethics Subcommittee is effectively functioning like an IRB--that the research design is sound. So after I talk about risk, I'll then run through a number of recommendations and stipulations that the committee made to assure itself that, in fact, the research was sound. But assuming those are made, the subcommittee felt that the following risks would be appropriate:

The first is the single dose of dextroamphetamine. Is that minimal risk? The feeling was no. We can a little bit later, if you'd like, about the definition of minimal risk, but, in fact, that was not minimal risk. But the subcommittee felt that it was no more than what's called a minor increase over minimal risk, and it lists the reasons there, which I think I'll state in more detail for highlight.

First of all, it has been used since 1937 with a good safety record. It is one of the only two stimulants that are approved down to age 3, and the children in this protocol are between 9 and 18. The greatest side effects are irritability, restlessness, agitation, and temper outbursts which generally last only 4 to 5 hours, are infrequent, and as you'll see later, one of our risk minimization strategies was to say they should do this in the morning so you don't have the kid up all night after you do this. It's used universally in pediatric practice, and the more common risks are restlessness, anxiety, loss of appetite, insomnia--again, why we made that recommendation.

There were two procedures we felt ought to--well, a second procedure that we felt ought to be drawn out and highlighted, and that's the withholding of medication for 36 hours from the kids with ADHD. The feeling was that also could be characterized as a minor increase over minimal risk. The reasoning here is that kids with ADHD often are not medicated over the weekend, often are

not medicated when they're not going to school, and are often given holidays from the drug. So it didn't feel that a 36-hour period of time was of any significant risk to those children.

And then the remainder of the procedures, which are outlined further along, we all felt were appropriately considered minimal risk and, therefore, were appropriate for either group within the protocol.

Now, the one design recommendation that we made was to consider narrowing the subject population that's part of this protocol. There was some discussion about the variability in both neurodevelopmental stages and then response to this dose of the stimulant between the ages of 9 and 18 years of age, with different points being raised as to the scientific advantages and disadvantages of either the younger age group or the older age group. We didn't feel that we could make this a stipulation, but felt that the investigators should strongly consider narrowing that range within 9 to 18 to get a more focused population.

The other confounder that came up--and this is also in response to some points made in the public discussion--is that trying to tease apart the changes that might occur in response to the drug over time versus basic underlying differences in terms of, if you will, the neurological networks, that you need ideally to have treatment-naive subjects with ADHD, or at least less ideally, if that is a practical difficulty in doing in this particular age group, try and get a more uniform cohort of drug exposure, which is why we had the discussion of picking the lower-dose range.

One reason for that was that the expert scientists felt that often the dose over time that you may need goes up, and if they unified the dose, then probably you would end up with a more uniform distribution of the length of exposure to treatment. But we didn't feel that that reached the level of a stipulation, but certainly felt that that was a strong recommendation to consider improving the scientific value of the study.

Now, there are a number of required

modifications to the protocol. Point A, which I'm not going to read, is basically my summary of all of the procedures in the protocol. And one of the recommendations is--it was very hard to find all of these things, and it would be nice if they just put them in one place so no one had to go reading through it in all detail. One, for example, that came up--and I'll just highlight this--is that every child will receive a diagnostic MRI scan, which is, in fact, part of NIH policy. You could find that nowhere in any of the documentation, and that came out during discussion. Things like that need to be in the protocol.

I might add, what we will be doing is depending upon both the Office of Pediatric Therapeutics and the OHRP to make sure this happens, so it's not something that we need to then worry about.

The second point, sequence of subject testing. They're not planning to do the kids that are twins. There are discordant twins, either both homozygous and dizygotic. They're not going to do

those twins unless they see differences between the kids with ADHD and the kids without ADHD. That sequence of testing, which came out in testimony, was very hard to find anywhere in the protocol, and that needs to be included. They won't do the twins if, in fact, they don't find a difference in the non-twins.

It was very hard to find the right dose since there were these dosing discrepancies, and so that needs to be clarified. But I've stated what the committee's understanding is, and, of course, if this is different--and this is based on the investigators' testimony--that will have to be dealt with. And, again, I mentioned the morning.

A functional MRI. The protocol lacks a discussion of what came out in the testimony of the training that goes on to make sure these kids are comfortable inside the machine, make sure they can actually do the tasks that they're being requested to do, et cetera, exclude kids from claustrophobia. Not much in the protocol about that. I already mentioned the diagnostic MRI scan, which needs to

be in there.

Pregnancy exclusion. You only found that in the parent permission form. The feeling was that that needs to be discussed in the protocol and the child assent documents, and in particular, mechanisms for protecting the confidentiality of the adolescent that she may or may not want to go into the protocol knowing that there's a pregnancy test depending upon activities. That needs to be spelled out. We weren't making a judgment about how that should be handled other than the importance of the confidentiality in soliciting that information.

There was a significance discussion of neuropsychological--I would like to have questions at the end, because what will happen is I bet you some will be answered, but write them down. Neuropsychological testing. There was a lot of discussion about this testing. It's not being performed for diagnostic or treatment purposes, and we felt it would be a cleaner study if, in fact, this information was not provided back to the

parents. Part of that discussion was based on it not being done in that kind of a therapeutic context.

And then genetic testing. There is testing being done only for zygosity, and we felt since there was a whole slew of markers being done and no discussion about the risk of those markers relative to, say, late onset adult diseases, that the cleanest way to do that would be to destroy the data and the samples after you've determined the zygosity of the twins, maintaining only that piece of information.

Modifications to the parent permission and child assent process in documents follow, of course, those that need to be included from the discussion of the procedures. There were a couple of specific issues. One is payment. They were proposing a lot of money--I didn't put it in here, but a lot of money. We felt it was too much and that basically the parents should get reimbursed for expenses, and that for young children, a token--although we didn't have a discussion of what that

is, but allowing the IRB to have some discretion, and for older children who would be potentially capable of working at a wage position such as minimum wage, the wage model would be appropriate. And, of course, consistent with FDA policy, this would be, in fact, divided evenly over the protocol procedures so that a child who withdraws in the middle still gets part of the money.

They needed to pay attention to the opportunity for dissent, particularly in the twin pairs. We thought that the twin without ADHD could be under some pressure to be in the study, and they needed to provide that opportunity. And then some clarification about the risks of the drug in the actual consent document, and in many ways we actually said you should overstate the risks in the consent document. Although we do not feel that this drug presents any risk of addiction, the parents should know that, in fact, it's classified as a drug of abuse, with an important distinction being made by our experts between substance abuse and addiction. It's one thing to say take

dextroamphetamine to be able to stay up for your exams in college, but that doesn't lead to addiction because generally you don't then want to take it when you plan to fall asleep during vacation. And, of course, both permissions.

Now, there were some specific questions that we were asked to respond to, and I think for these questions, perhaps I'll just read our answers so that you get it clear.

What are the benefits, if any, to the subjects and to children in general? There is no direct health benefit to the children included in the research. The protocol addresses the question of a unique central response to stimulants in ADHD, utilizing a better research design than previously published studies and controlling for performance differences. As such, the protocol may be able to untangle clinical state and trait--meaning genetic relatedness--differences through the use of monozygotic and dizygotic twins who are discordant for ADHD. Now, more speculatively--and this was part of the discussion--the results may improve our

understanding of ADHD in order to enhance diagnostic precision and avoid misclassification and overtreatment.

Now, the types and degrees of risk that this presents to subject, I've discussed a fair amount of that above, and, again, we thought that all of the procedures other than withholding of the medications and the blind administration of study drugs were minimal risk, and those two were a minor increase over minimal risk.

In terms of whether the risks are reasonable in relation to anticipated benefits, this is a key point. For all subjects enrolled in the research, the risks to subjects are reasonable in relationship to the importance of the knowledge--i.e., the benefit to children in general--that may reasonably be expected to result. However, it is only for the children with ADHD that the research is likely to yield generalizable knowledge which is of vital importance for the understanding of the subjects' disorder.

For you regulatory junkies, you'll know

that I'm reading language that is contained within the regulations as well, but the important thing is then that children without ADHD do not have a disorder or condition, which is why this then could not be approved by the local IRB, although the brain response of children without ADHD to a single dose of dextroamphetamine is an important part of the generalizable knowledge to be gained in this research based on the first step of the comparison.

So we thought it did present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

So, with that said, the determination of approval categories that the subcommittee felt was appropriate was that the interventions and procedures included in the research can be approved for the children with ADHD under 45 CFR 46.406 and 21 CFR 50.53. That's the category that says no more than a minor increase over minimal risk; that basically the experiences are reasonably commensurate with those inherent in their

condition; the intervention is likely to yield generalizable knowledge about the subjects' disorder or condition, which is true for the ADHD; and then that there are adequate provisions for assent.

Now, because of the lack of a condition in the kids without ADHD, we felt that it could not be approved under those three categories consistent with what the IRB found. But we did feel that it presented a reasonable opportunity to further the understanding of a serious problem; that it would be conducted in accord with sound ethical principles; and that there are adequate provisions for soliciting assent and permission. And as such, we recommend that the involvement in the research of children without ADHD is approvable, assuming all of the required modifications are made, under 46.407 or 50.54.

Then one final point. It had been brought up in some of the public testimony, the applicability of a particular case known as Grimes v. Kennedy Krieger Institute. Whereas, normally or

often we might anticipate that the kinds of studies that come before us are going to be multi-institutional, multi-site, and multi-state and we're not going to want to get into the business of commenting on the legal interpretations of all of those different environments, we have the unique situation here where this is a single site located within Maryland, and this is a fairly high profile court decision. So prior to the meeting, I had asked for clarification by both FDA and OHRP attorneys about the applicability, and the feeling, which I agree with and I think some other knowledgeable members of the subcommittee that I've talked with also agree with, is that the holding is not applicable for two reason: One is NIH is a federal enclave and not subject to state law; and second is when this case was considered, reconsidered, the Maryland Court of Appeals stated that "the only conclusion that we reached as a matter of law was that, on the record currently before us, summary judgment was improperly granted." So attorneys have a term called "dicta,"

which means basically the judge expressed opinion on other matters, but, in fact, those other matters are not binding as law. So for those two reasons, it was felt that we did not need to get into the issue of the applicability of this particular case as a subcommittee.

So, with that summary, I guess how about questions about the document, the protocol and the like, and then after that, I certainly would be interested in any more general questions about the process, if that's a reasonable approach.

T1B

DR. CHESNEY: We actually have a visitor this morning. Dr. Bern Schwetz is the Director of the Office of Human Research Protections, and I wondered if we could call on him to come and make a few statements before we invite questions.

DR. NELSON: Sure.

DR. SCHWETZ: Thank you very much, Dr. Chesney. I just wanted to express my thanks for FDA and this Advisory Committee creating the opportunity to do this joint review in one process rather than have the FDA and OHRP going in separate

ways to review a protocol of this kind where there's joint jurisdiction. So particular thanks to Dr. Nelson for chairing this review and this subcommittee. In our opinion, the process went as we had hoped it would, with a very smooth review, but probably more importantly, a thorough review and a recommendation that we feel is a good recommendation coming to this Advisory Committee for your final review and hopefully approval.

The review was done in a timely manner, and that was a challenge considering that this is a new committee, a new subcommittee, but it was done in a timely way. And I think it was done with an appropriate cast of experts. So we're very pleased with this process and, Dr. Chesney, with your permission, we're hoping that in those cases where we have joint jurisdiction over a protocol in the future that we'll be able to bring it back and handle it this way.

So thank you very much.

DR. CHESNEY: Thank you for your comments, and maybe you could stay here just for a moment,

and we'll ask now for any questions of the new committee members for either Dr. Goldkind, Dr. Nelson, or Dr. Schwetz.

Dr. Maldonado?

DR. MALDONADO: I just have a quick question. Dr Nelson, I see that on page 1 you made the statement--and I basically also agree that you did a great job with this review. You listed the minor increase over minimal risk, which I agree are just a minor increase. But then on page 2, you gave a--maybe I am just overreading this, but the subcommittee strongly encourages the investigators to narrow the age. I know you focused on that, and I may have missed it. My understanding is this is a single-dose study. I don't know what the concerns will be with single-dose for neuro-developmental stages with a single dose, low dose.

DR. NELSON: The issue is not the impact of that dose. There might be a response difference that you could see, but the question is teasing apart--there is a debate on previous studies that have been done of structural MRI scans, and there

are actually two previous studies of functional MRI scans where the question is whether or not some of the differences that may be seen are not related to any underlying biological differences, neuro-developmental differences, but, in fact, the kids with ADHD had been chronically exposed to a medication which--I'm not a neuroscientist. I guess I would characterize it as whether it's created some element of remodeling of those systems. And so try and eliminate that confounder, the feeling was if they would narrow the age range and then try to either get treatment-naive, which may be difficult, or at least treatment-uniform at lower doses which would give you hopefully a lower duration of exposure, that you might be able to begin to tease apart those two issues. That was the scientific discussion among the experts.

DR. CHESNEY: Yes, Dr. Fant?

DR. FANT: Yes, this question may be a bit naive, but it quickly comes to mind, especially from the standpoint of taking the kids off the meds for a couple of days and trying to ensure treatment

naivete and the question that that may have on their response.

And so the question is: Are there any over-the-counter stimulants or food additives that could potentially interact with their response and somehow muddy the data? And if so, is that being controlled for or addressed in the protocol?

DR. NELSON: The answer is yes. I mean, one of the discussions, of course, by the IRB was whether caffeine and the element of caffeine consumption could be used as a judgment. So there are some confounders and the need to collect that data, and it would be sort of self-defeating if over the weekend you take the kid off of his medication and then he drinks, you know, a couple of cases of Jolt Cola--which I don't even know if it's still made or not. I have no stock in that company. No conflict of interest on that recommendation. Or Mountain Dew. I think Mountain Dew has a lot of caffeine in it. So, yes, they need to pay attention to that.

DR. FANT: And even with adolescents who

may be concerned about weight and appearance and that sort of thing, some of the additives that are contained in supplements in GNC at the mall, you know.

DR. NELSON: Right.

DR. MURPHY: So, Dr. Fant, was that a question or just a recommendation, I guess is what I--

DR. FANT: Well, it's a concern because if we're talking about giving a drug to, quote, normal kids, you really want to ensure that the data is as clean, as interpretable as possible. You wouldn't want to muddy the waters on something that could have easily been avoided.

DR. MURPHY: I think that, you know, if there are recommendations that this committee would like to make, that's appropriate. And we wanted to make sure that that was--

DR. NELSON: I see that as just a refinement of the recommendation to make sure your subject populations are as uniform as possible. So it's certainly consistent with our direction.

DR. CHESNEY: But we maybe should add a sentence or two, Skip, just to--I thought that was an excellent point if somebody does--I don't know how long those stay in the bloodstream, but if that's their breakfast and then they show up for the fMRI, there may be a confounding variable.

Yes, Dr. O'Fallon?

DR. O'FALLON: Did you recommend that they collect that information?

DR. NELSON: No, but we can add a sentence to that.

DR. O'FALLON: Okay. I think it would be helpful to make sure that they elicit that information.

DR. CHESNEY: Deborah, you were next.

MS. DOKKEN: I first want to compliment Dr. Nelson's subcommittee. I mean, not only did you do a thorough job, but I could fully understand what you were talking about, and I was glad that you included the issue of compensation and the potential pressure on the twins in the assent process.

I was also glad that at least in some way you directed attention to the permission and assent forms and talking about the chronology of the procedures. But I had a further question about those forms, which, frankly, I don't know what their rating is in terms of reading level, et cetera. But they certainly to me were not easy to read and, in fact, were mixed. Sometimes they used almost simplistic language; then you know, the next sentence--did you talk at all about just the forms themselves and the language beyond the chronology issue?

DR. NELSON: Yes, we did. But that's just captured on page 5 under age where we just say there's technical language would is not explained in lay terminology.

I think two points on the process: A, this still then needs to go back through the NIMH IRB, plus it has two offices, not just one now, that will recognize that for this to be finally approved would require that kind of changes in the documents. And I'm absolutely confident that with

OHRP and FDA's involvement in making sure that these requirements happen is that they will be in more understandable language.

My own philosophy is there's no reason for us to sort of nickel-and-dime the actual text, but that was discussed.

DR. CHESNEY: Could I just add, there was a great deal of discussion about the protocol and about the consent form, and, in fact, one of the committee members asked if this was a draft of the consent form. And the folk from the NIMH apologized and they said that they got so busy addressing the issue of whether this would have to come to a subcommittee that they hadn't really paid that much attention to the consent form, but that they would do that.

Dr. Newman?

DR. NEWMAN: I also want to compliment the committee on a really very impressive, thorough review. And I have three points. One is just a clarification.

Looking on page 7, comparing Parts a) and

b), under--I'm just trying to figure out how--I have reservations about the value of the research to kids with ADHD. I really--it's very hard for me to picture how this research will be useful, but maybe that's just due to my limited scientific knowledge. It says under C, the procedure is likely to yield generalizable knowledge about the subjects' disorder or condition, which is vital importance for the understanding or amelioration. And I really couldn't go along with this being of vital importance. But then under B it says it presents a reasonable opportunity to further the understanding, and I could go along with that. So I'm not clear on which of these two is the standard that this research has to pass.

DR. NELSON: You point out an interesting ambiguity in the regulatory language for which there is no specific guidance about how one interprets "vital importance" or "reasonable opportunity." My own view is that it needs to meet both, that you would not want reasonable opportunity to be a lower standard. And the issue

of vital importance is fundamentally subjective. And from that standpoint, there was a recognition--and that's why I put earlier on the notion that more speculatively. I mean, this is what--I would characterize this as sort of a basic science question about the response and the neuro-developmental sort of receptor physiology.

If, in fact, there is no difference, it would have an impact significantly on the understanding of ADHD, and if there is a difference, it would impact significantly, and then might, not in this protocol but down the line, potentially drive diagnostic and therapeutic differences. One thing I learned is there are individuals who are touting different structural scanning tools for diagnosis of kids with ADHD, et cetera, that many felt, in fact, were not evidence-based. And so after hearing that discussion, the subcommittee members felt that it did meet the regulatory standard both for vital importance and reasonable opportunity.

There was no, if you will, easily defined

paradigm for that.

DR. NEWMAN: Okay. Well, that sort of leaves me uncertain. Let me go to my next question, which was in the consent form they specifically addressed the issue of potential adverse effects of the MRI in terms of identifying some little something which then people go, oh, we wonder what this is, maybe you should go have that checked out, but that not being covered by the research study and the family may or may not have medical insurance to cover that. And I believe that's more than minimal risk. That's something well beyond the range of what people experience every day, the possibility of having some brain abnormality uncovered, which then you have to figure out how to deal with. So I wonder why that wasn't considered, you know--

DR. NELSON: It was. I didn't include it in here because the data actually is that out of 3,000 scans, they've only found four abnormalities. And of those four, two were benign cysts and two were actually early diagnosis of tumors where the

child benefited from that. So there was a discussion in the subcommittee about the implications of using a screening test in a population that--you know, being a statistician, you can understand the sensitivity and specificity issues. But after that discussion and the fact that it's being conducted--it's not a diagnostic reading of the functional MRI. It's a separate diagnostic MRI scan that, after hearing the discussion, we felt that it was appropriate to consider that under that category.

So they have enough data, I think, to sort of--at least reassure me that they're not going to be turning up a lot of things that end up with unnecessary testing.

DR. NEWMAN: If I were a parent trying to make an informed decision about participating in the study, those data would be very helpful to me to know what--to say this may happen, but they don't give any numbers on how likely it is to happen and what might be found. And so, you know, I just think it's hard to ask someone to consent to

something, you tell them that risk, but you don't tell them how big it is. So I think that would be helpful for them.

And my last question was just about the financial compensation. For the controls, you know, it sounds like this may take several hours out of the parent's day, and so, you know, having tried to get people to enroll in studies before, you know, I don't know whether there have been pretests or what it would take. But if you're going to ask someone to bring their normal child in and get a lot of stuff done, you know, to me I think maybe $100 or $110 split between parent and child might not be enough to get people to want to enroll.

DR. NELSON: No, it was not split between parent and child. That would be wages for the child, and the investigator actually said--and this did influence the committee--that she did not anticipate any problem with enrollment even if the compensation and stipend was zero. I'm just telling you, that's what she said.

DR. CHESNEY: Could I just also comment for Dr. Newman? It was suggested that they publish the fact that they had only four abnormal MRIs out of 3,000, which is certainly not within the realm of most of our experience where MRIs show you all kinds of things that you don't want to know. So that suggestion was made.

We had a lot of discussion about the science because it's a very--to me it was a very complex study to understand, and a lot of it was based on the study by Viga (ph) et all that was published in '98 or '99. And I thought--it wasn't until the very--long into the meeting that Dr. White, who's a child psychiatrist with a lot of familiarity with functional MRI scanning, pointed out the importance difference with respect to the performance task in this study as compared to the one published in '98 or '99, which had led to perhaps some erroneous conclusions.

So I think that after a lot of discussion we finally became convinced that the science was important, if that's of any help.

Any other questions or comments? Dr. O'Fallon?

DR. O'FALLON: I was just wondering about the pregnancy exclusion. I didn't look at the consent form closely enough to see. Presumably they are excluding on the basis of pregnancy. Is that it?

DR. NELSON: They are. It wasn't very well described in the consent form, which was our point.

DR. O'FALLON: Okay. Well, but that's the point. So they have to--so they do have to take this--they have to have a pregnancy test. Now, I'm just curious. How do they think they're going to--I mean, how do they plan to deal with exclusion basically on pregnancy alone when they don't--they can't tell it to the parent?

DR. NELSON: They didn't outline that, but, I mean, I'm confident that they can come up with a procedure. We're just asking them to do that, and I'm sure OHRP will make sure it's a good one.

DR. O'FALLON: Okay. I wonder how they are going to do it.

DR. CHESNEY: Very important points.

Any other--Dr. Newman?

DR. NEWMAN: Let me just explain what my reservations are about the value of the research, and maybe you can reassure me. It seems to me that ADD is a clinical diagnosis, and in making the diagnosis, one of the main decisions that you're trying to guide is whether to begin stimulant medication. And if you begin stimulant medication, you want to see whether it helps the child and monitor that and discontinue it if it's not working and continue it if it is.

And I just cannot visualize how an MRI scan would ever sufficiently predict a child's response to medication to be clinically useful, because, I mean, they may well find some statistically significant differences where the something or other is, you know, a half a standard deviation different in one group than the other, or maybe they're quite different. But the fact is

whatever they find, the question is really whether this child would benefit from treatment or not. And, you know, the way you determine that is whether--either trying the treatment and seeing if it helps, or if you were going to do a study to see whether imaging helps, you would see whether imaging predicts response to treatment, not whether imaging predicts or is associated with someone having received this clinical diagnosis.

So I am a little bit worried if it does show a difference that this will spawn a whole imaging industry of people wanting to get their children's heads scanned to see whether they really have it or not, which I think would just be going in the wrong direction.

DR. NELSON: I guess two comments. This has nothing to do with the clinical response of the children. There is no benefit. It has nothing to do with that. Whether or not it--if it does show a difference, appropriately designed, it would spawn a functional MRI industry I think is speculative and, in fact, is explicitly, if you at Subpart A,

excluded from what an IRB ought to consider. The long-term policy implications of research is not something that IRBs are supposed to consider, and I wouldn't necessarily import it under vital importance.

The question is whether or not there are structural or functional differences, and presumably based on receptor density, et cetera--it's not my area so I'm just saying things that you could have read in the protocol and listening to the scientists. And as a basic science question, I think that's an important one. And how it might then impact down the road in terms of understanding whether there's a differential or similar response to stimulants, I mean, the literature is quite mixed in terms of reading some of the background material in the protocol.

So there is no connection in doing this with determining why they might respond clinically. There is no--and, in fact, many of our recommendations were meant to prevent that confusion from being in the minds of the participants by

removing any semblance of benefit from the sort of surrounding aspects of the science. But, you know, I think ADHD is a controversial area, and it's partly why we felt this needed to be looked at carefully and then done well, because I think the positive or negative results could have an impact in different directions.

DR. CHESNEY: I think Skip expressed it very well. The purpose of the study was not to have any clinical diagnostic value or clinical implications. The purpose of the study is really to understand, as Skip said, the neurophysiology and neurochemistry--to try to understand the neurophysiology and neurochemistry of ADHD better, and because of the twin aspect, to see if there are any genetic aspects.

Dr. Maldonado?

DR. MALDONADO: A quick question that goes beyond this study, but it's in the context of ADHD. One of the premises that I think a lot of researchers' work is under that if the studies can be done in adults, don't do it in children. And

now adults are being diagnosed with ADHD. Has something similar been done in adults or can be done in adults, you know, consenting adults, so you don't use this area of consent of children?

DR. NELSON: Two points. That specific question was raised by the subcommittee. There have been similar but not identical studies, but it's clear that the adults are different in this regard and that the information that you would get would be of no use to this issue. And that discussion actually is why you may even--in the discussion it was clear that the scientific arguments might push you in the direction of using actually the 9 to 12 age group as opposed to the older age group because there may even be those kinds of adult changes when you get into sort of late adolescence. But we felt that that was not clear enough that we would make a stipulation as opposed to recommendation.

So I think that is an important principle, and it was asked and answered in the negative, that adult information here would be of no use to

answering this question.

DR. CHESNEY: Dr. Schwetz, did you have any additional comments about the questions from the committee?

DR. SCHWETZ: No, I don't have anything else to add. Thank you.

DR. CHESNEY: Dr. O'Fallon, you look like you were--

DR. O'FALLON: I hesitated simply because--but I'm a mother and not an M.D. I've had an MRI. I don't know what--for my neck. I was wondering what a functional MRI for the brain involves for the child.

DR. NELSON: Nothing different than an MRI scan.

DR. O'FALLON: But the question is they are enclosed, so there is the issue of claustrophobia?

DR. NELSON: Correct, but they have screening procedures for that. There's no issue in that. The kids are actually less claustrophobic than the adults.

DR. MURPHY: Skip, why don't you describe the screening procedure--

DR. NELSON: They have a training MRI scan which is--and they make--you know, first they've got to make sure the kids can do these tasks, so they use the stop task and a training MRI scan. They have a whole sort of session. I mean, everybody--if a kid doesn't want to do it, then that's the end of it. You know, their procedures are excellent with respect to that. The issue is not that they're not doing it. The issue is they just didn't describe it in the protocol. They described it quite completely in the discussion on Friday.

DR. MURPHY: I think as a risk what you're trying to get at is that those kids that are going to have that impact of anxiety, psychological fear, will be--will not be enrolled. In other words, that's where the screening procedure would help select those children out.

DR. O'FALLON: Yes, but, of course, the screening itself could cause this--I mean, they

could precipitate this anxiety. I don't know what--at the time of my MRI, I was told that there's a fairly high percentage, like 25 percent of adults, anyway, that experience--well, that's what I was told, when I was told about it, that experience claustrophobia.

DR. GOLDKIND: Could I speak to that? They actually show the kids a video, and they have a very well organized approach, even before they do the screening program that was described to us on Friday. Additionally, they said that because children are smaller than adults physically, they are not as confined. They don't have the feeling of claustrophobia that adults do based on physical size and also based on psychological orientation. Generally speaking, children don't have as high a claustrophobia rate as adults do.

So for all those reasons, the subcommittee felt that it was a minimal risk intervention. And then as Dr. Murphy said, if a children demonstrates hesitation at any step along the way prior to getting to the actual enrollment, they're excluded.

DR. NELSON: Twenty-five percent sounds quite high to me, anyway, even for adults.

DR. O'FALLON: Maybe it's because of the practice of ours. We have a whole lot.

DR. CHESNEY: Let me ask, not seeing any further hands being raised, does the committee feel that they are comfortable endorsing this summary of the events of Friday? We're not required to take a vote on this. Unless there is somebody who is not comfortable endorsing this, we would like to pass on to Dr. Murphy the committee's endorsement.

[No response.]

DR. CHESNEY: Not seeing any hands being raised, I think that we can--yes, Dr. Nelson?

DR. NELSON: I just want to ask, you know, in terms of adding the issue of collecting data and trying to exclude caffeine and other stimulants under the design recommendation and the discussion of the communication of the risk of inadvertent findings on the diagnostic MRI scan, can that just be made by office staff? Or do you want me to just do it myself and give it to you?

DR. JOHANNESSEN: We can do that.

DR. NELSON: Okay.

DR. CHESNEY: Thank you very much, Dr. Nelson, for chairing this--

DR. MURPHY: We have one more question over here. Would you like to please identify yourself for the committee and ask them this question?

DR. STITH-COLEMAN: My name is Irene Stith-Coleman from OHRP. What I would suggest is that if--in terms of the additional statement, could you clarify if you recommend that it be a recommendation or stipulation? That would be of help to OHRP.

DR. NELSON: The first one about caffeine or other stimulations is going to go under the design recommendation, not stipulation. And then the comment about communication of risk, one of our discussions at the meeting was whether they, you know, have all the data, but I think the recommendation that they communicate that information in a meaningful fashion to parents

would go under the diagnostic MRI scan, which fits under a stipulation. The only thing that's a recommendation to consider, which they could then come back with arguments for or against, is number 3. Everything else is stipulations.

DR. MURPHY: That was helpful. Thank you. This is a new process. As Dr. Schwetz said, we're very enthusiastic about the fact that we aren't setting up a process that would almost engender or increase the possibility of having differing recommendations if you empanel two different groups and have two different sets of experts. There's always a probability that you going to get two different sets of answers. So I think that-- however, it's been very helpful to hear the comments from this group, and I think that at this point, Dr. Schwetz, what we need to make a cut on is where recommendations would just go straight up forward via both of these mechanisms versus if there were some major concerns, what we would do in that situation. I think we're not at that level right now, but that is certainly something we would

want to consider for the future.

Skip?

DR. NELSON: Just one other point that I think, as word goes out, might be surprising to many IRBs, although I realize that it's, in fact, the correct interpretation of the regulations, many IRBs do not think simply because you're using an FDA-regulated product in a clinical investigation or in the research that it's an FDA--that the FDA has oversight. You know, both of these products are being used in accord with clinical recommendations at doses that are being done clinically. And I think that to many IRBs might be a surprise. So just to alert you to that as this word might trickle out. I do know that the FDA does have jurisdiction, even if it's an approved drug being used in a clinical investigation. But many IRBs don't think that--or don't know that, I should say.

DR. MURPHY: And it's new for the agency, so actually it's something that we are making sure everyone within the FDA is aware of also. So I'll

just give you that sort of forewarning.

DR. CHESNEY: Thank you very, very much to everybody who prepared for Friday's presentations and for the process, Dr. Nelson for chairing it all, and Dr. Schwetz and the other members of the OHRP who were there, but who also took the time to come today. We very much appreciate your time. And thank you to the committee for your questions. They were very, very perceptive given that you hadn't been at the meeting Friday. You really raised some very important and additional issues.

I think I will move on to--

DR. MURPHY: I just have one last person I wanted to thank, and that's Terry Crezenzi (ph) and Sara Goldkind, working with OHRP, spent many, many, many weeks and months putting this process together, and just because she made the terrible decision to leave us and go on detail elsewhere, I wanted to make sure we recognize the contributions that she has made to this process.

Thank you.

DR. CHESNEY: Thank you. We don't know

about all the behind-the-scenes work, so thank you very much for clarifying that.

All right. Well, moving on to the next section of today's meeting, let me introduce Dr. Solomon Iyasu, who is a pediatrician and medical epidemiologist. He was with the CDC for 13 years leading the Infant Health Program there. And here at the FDA, he's a medical team leader in the Division of Pediatric Drug Development and a medical epidemiologist in the Office of Pediatric Therapeutics. I don't know how you all keep track of who you are.

Today's talk will provide an overview of the BPCA mandate for adverse event reporting, the review process, and FDA's adverse event reporting system. Dr. Iyasu?

DR. IYASU: Good morning. It's a pleasure to be here and present to you the adverse event report for several products that have been given pediatric exclusivity.

The Best Pharmaceuticals Act for Children, which was enacted in 2002, does have a provision

for mandatory reporting of adverse events for products that have been given exclusivity. Under Section 17 of that act, FDA is required to review adverse event reports during the first one year after exclusivity is granted to a particular product. And once that review is done, then the FDA will report a summary to the Advisory Subcommittee, which now is a full committee, for their review and recommendations.

The review process that we have implemented at FDA for drug products includes a very close collaboration between the Office of Drug Safety, which does the primary review of the adverse events reported for the one-year period, and then also the Division of Pediatric Drug Development, who would be participating in this review, and then finally the Office of Pediatric Therapeutics, which is the new office which has overall responsibility over adverse event reporting for pediatric issues.

Just to outline to you what we've been doing over the last two years in terms of the

review process, we have implemented sort of a process which includes and defines responsibilities for each of the participating offices. The Office of Drug Safety has responsibility for reviewing the adverse events reported during the one year and also has responsibility for immediately discussing any serious unexpected events including deaths with the Office of Pediatric Therapeutics and also the Office of Counterterrorism. And, finally, it has a responsibility also for submitting the written safety review and sharing them with OCTAP, which is the pediatric group, and the Office of Pediatric Therapeutics, and, more importantly, with the review divisions that are responsible for these particular drug products.

Then OCTAP, which is Office of Counterterrorism and Pediatric Drug Development, and OPT have joint responsibilities for also notifying the Office of Drug Safety once exclusivity determination is done for any products, so that the tracking could start then for a period of one year after that date of determination.

The medical officers within these two office also have roles in reviewing the ODS reports that are submitted, and then also looking at the individual adverse event reports, the MedWatch reports, and also preparing summaries and presentations for this committee.

We try as much as possible to focus the adverse event presentations on issues, safety issues that may have arisen during the review process so that the committee's time is better spent on important issues.

We have also developed, in collaboration with the Office of Drug Safety, a template for summarizing the review, and the safety review includes an executive summary that sort of highlights what the issues are from the review. We also include in that template a review of the adverse event reports for adults and pediatric patients from the original drug approval date up to the time that the drug has been reviewed for the exclusivity process. So it's a longer view, but it's an overview, really, trying to see what the

number of reports have been for adults and in pediatrics, and also trying to get a handle on whether--how many of them were actually U.S. origin and how many of them are actually foreign reports.

Then for the more focused pediatric review, we have a detailed template which I'm highlighting here were the issues of the specific reviews that are done by the Office of Drug Safety. We expect counts and labeling studies of the top 20 most frequently reported adverse events within the pediatric population as well as adults, but we focus more on the pediatric issues. We also try to get from the MedWatch reports the summaries of the demographics, age, gender, distribution of the adverse event reports for the one-year period, including a description of the serious outcomes, indications, and doses that may have been associated with these adverse events.

Then there is an evaluation of whether these adverse events reported during the one-year period are unexpected events or are they unique to pediatric patients and not reported in adults. So

there's an evaluation that's done sort of comparing adult and pediatric reports.

Also, an evaluation of whether there is an increased frequency of non-pediatric adverse events in this population, but this is done for the one-year period. And then, finally, sort of developing adverse event profile for that particular drug product, which will then sort of highlight what the issue is, if there is an issue that has developed during that review process.

We also have for the denominator data, trying to understand what the exposure us in the pediatric population, we use various databases that are available to FDA, which I'll briefly describe later on, which estimate drug use in the outpatient setting for this drug product, as well as for the inpatient population.

The role of the Pediatric Advisory Committee is really to assess and discuss the presented adverse events. We've been doing this now for almost two years. And if appropriate, recommend additional pediatric review and/or any

regulatory action if deemed appropriate.

T2A The role is evolving. This is a new committee, and there may be other responsibilities or even roles that would be defined as we go into having more experience with this process.

Now, I want to sort of give you a brief overview, top-line view of what the adverse event or the Postmarketing Drug Surveillance Program includes and the various components that may be tapped to assess drug safety. The cornerstone about this is, of course, the passive surveillance system, which you've heard about so much in previous presentations, which is the Adverse Event Reporting System, which includes adverse event reports, spontaneous reports, and manufacturer reports that are sent to FDA.

I also mentioned sort of the--on the denominator side sort of trying to assess exposure, the drug utilization databases that FDA has access to, which include outpatient, inpatient, and some longitudinal data.

Other databases that may be tapped also

for evaluation of adverse events, external health care databases which may includes claims databases from special populations or from the general population, and then there is also information sort of a repository of background incidence rates on different adverse events or conditions that may come from hospital discharge surveys or from the literature that we may actually tap in our evaluation.

Then, finally, there are some active surveillance systems that look into possible drug-associated adverse events. I'm not going to go into detail about this, but the DAWN is the Drug Abuse Warning Network, and then NEISS is the National Electronic Injury Surveillance System, which is run by CDC, and TESS is the Toxic Exposure Surveillance System, which is run out of the Poison Control Centers.

Now, just to give you an overview of the most pertinent one, which is the AERS database, as some of you probably know. It originated in 1969 as the Safety Reporting System. It currently

contains more than two million adverse event reports in the database, contains drug and "therapeutic" biologic adverse event reports, with the exception of vaccines which has a separate reporting surveillance system.

Just to give you some idea of what reports are, they are mostly voluntary/spontaneous reports that may come from health care professionals, consumers, patients, or others. But also a large majority of them are actually mandatory reports that come from manufacturers required for postmarketing reporting purposes by law. All adverse drug experience information obtained or otherwise received from any source, foreign or domestic, will be included in this. And to give you more detail, there will be more detailed discussion later on about this.

But in 1993, the whole Adverse Event Reporting System was redesigned and the MedWatch form was developed. You probably can't see this slide, but in your handout you probably can identify some of the design aspects of the MedWatch

system. But, in short, this is the form that unifies in terms of reporting for drugs and also for biologic products and also for devices and dietary supplements.

Now, by law there are definitions for different kinds of reports. What manufacturers must report is defined under 21 CFR 314 that includes all adverse event reports from commercial marketing experience, postmarketing studies, and scientific literature. And this may include all domestic spontaneous reports that must be reported to the FDA. In terms of foreign or literature reports, all serious, unlabeled events are mandatory in terms of reporting. And it may include also study reports which may be serious, unlabeled, or any adverse event with a reasonable possibility that the event may be related to a drug product.

Adverse drug experience is also defined by the regs. Any adverse event associated with the use of a drug, whether or not considered drug-related--this is an important point--has to be

reported. This may include accidental or intentional overdose or occurring from abuse or drug withdrawal or failure of expected pharmacological action.

Now, I mentioned before the serious adverse events, and there is a regulatory definition as well for this: any event occurring at any dose that results in any of the following outcomes. And this has been mentioned several times in yesterday's presentation. Some of you were not there, but this may include deaths or life-threatening adverse events or something that results in hospitalization or prolongation of hospitalization or persistent/significant disability or may result in a potential congenital anomaly or birth defect or requiring intervention because of an adverse event associated with a drug.

Also, there's a definition also according to the regs for unexpected adverse drug events or experience: any event not listed in the current labeling of the drug product, including events that may be symptomatically and pathophysiologically

related to a labeled event, but differ because of greater severity or specificity. So examples may be like hepatic necrosis versus hepatitis. So there is a regulatory definition as well for those.

Now, just to briefly go over the strengths of the AERS system, it includes all U.S.-marketed drug products. It's simple because it's passive surveillance. It's less expensive than having an active surveillance system, which may be very expensive. It provides for early detection of safety signals, and especially good for rare adverse events.

There are some very significant limitations of the AERS system. Underreporting is a serious problem, but this varies from drug to drug and also over time. Reporting may be more during the early phases of the marketing and may taper off later on. If there is media attention or public attention on a particular safety issue, reports may go up. Or it depends on what kind of drug it is, whether it's OTC or prescription drug. You may not get as many reports for OTCs and so on.

So there is a problem with underreporting.

Then there are also issues about quality and completeness of reports. That also varies, it often may be poor. You may not get information maybe that would help you assess temporality of the drug exposure with the event. You may not get information on concomitant medications or may not get very good medical history of the patient from whom the adverse event is being reported. So that is an issue which is sort of common to all passive surveillance programs.

Another important aspect in terms of limitations, the limited ability of the system to really estimate, help estimate true adverse event risk rate because the numerator is uncertain because of underreporting, which I mentioned, and also the denominator must be estimated or it's projected from sort of drug use databases that we have, virtually--may be difficult for some inpatient or OTC drugs.

I'll just briefly go over the outpatient drug use. I'm doing this for the benefit of the

new members to sort of give you what the sources are. For outpatient drug use, we mainly tap into the IMS Health System. One database is National Prescription AuditPlus, which provides an estimate of the number of prescriptions from retail pharmacies. The point on this limitation is that it does not include information on gender or race or age. So the information is limited, but it can give you an estimate of what the outpatient prescription volume is.

The other database, which is also an IMS Health product, is the National Disease and Therapeutic Index, which is a survey of 2,000 to 3,000 office-based physicians and really measures mentions of drugs during that encounter and includes a variety of specialties. But one disadvantage is that the diagnosis cannot be linked to the drug use. And the projections may be unstable, especially when use is very limited in some pediatric--for some drugs in the pediatric population.

Another source for outpatient drug use is

the National Sales Perspectives, which is also an IMS product. This is really a measure of the volume of drugs that are sold from the manufacturers to various distribution channels. This may include retail outlets and non-retail outlets. This is sort of a surrogate for use if you see that what is actually moving to the retail pharmacies or channels is really representing what is actually being used by patients. But also an important limitation is that we don't have information on age and gender in this database, so we're not able to be more specific.

For inpatient drug use, we have several databases. One is AdvancePCS, which is based on a large prescription claims database of the insured population. That includes about 75 million patients. But we don't have a projection methodology to sort of estimate it on a national level.

Premier is another database which comes from approximately 450 acute, short-stay, non-federal hospitals. The projection methodology is

available. It may not be very good for some drugs, so it is selectively appropriate in terms of making national projections. Again, the estimates cannot be linked to diagnosis or any procedure, and importantly, it misses the drugs that may be administered at the hospital outpatient clinics, especially come to mind oncologic drug products.

The last database that we have utilized is Child Health Corporation of America, which includes really just pediatric hospitals, and the data come from about 29 free-standing children's hospitals distributed around the country. An important limitation is that this is--we don't have a projection methodology to estimate at a national level, so whatever we get in terms of this database, although it may be specific to the pediatric population, is not representative of what the national experience may be.

Now, having gone over this overview, I just wanted to touch upon the drug products that we've reported on under the mandated BPCA review process. We started our first presentation in June

2003, and we covered several products at that time. The second one was October, the third one was February, and then June. So we've had four major adverse event reporting that we've done for over maybe 22 products, and today's presentations will be an extension of that.

Just to give you examples of some of the outcomes of the prior Pediatric Advisory Subcommittee meetings, we've discussed very important issues including SSRIs and SNRIs in relation to suicidal behavior and then class labeling for neonatal withdrawal, again, with SSRI products. That was actually a subject of discussion in the last AC meeting, subcommittee meeting. And then we have also discussed the fentanyl transdermal products, which have been associated with inappropriate use that may have resulted in some pediatric deaths, and there were some specific recommendations that were provided by the subcommittee for FDA regarding these drug products. So the mandated adverse event reporting has had important implications in terms of focusing

our attention on some of the safety issues. Despite its limitation of being just for one year, it's really brought attention to looking at safety issues in the pediatric population.

Now, just to give you an overview of what is going to happen today the way it's laid out, we are going to have presentations on several drug products, as you can see in the agenda. Dr. Hari Sachs is going to be presenting the one-year adverse event reports for ofloxacin, and alendronate, and Dr. Susan McCune will be presented on adverse events regarding fludarabine, and Dr. Jane Filie will be presenting on desloratadine. And then we'll have a break, and in the next section we will have several presentations which I will introduce later in more detail, but we have adverse event reports for fluticasone- or budesonide-containing drug products. And there will be a one-hour slot for this presentation. In regard to the drug products containing fluticasone, we'll be addressing that.

There is also a question that we have for

you to consider, so I wanted you to think about this while the presentations are going on. We'll ask you this question, and then we'll be very looking forward to your recommendations regarding these products.

DR. CHESNEY: Thank you very much. That was extremely helpful to me, reviewing the databases. You've probably done that many times before, and I didn't remember, but it's very, very helpful.

Any questions from the committee? Yes, Dr. Nelson?

DR. NELSON: I agree you've taken a system that doesn't provide a lot of data and tried to make it as best as possible. I guess this is a comment that perhaps at some future meeting we may want to discuss what we could do in the future perhaps to try and get a better handle on safety. The reason I'm concerned is if you think about the expanse of the past two days, all of those drugs were labeled for suicide as an adverse event, and most individuals, apart from the signal that came

out of the requested exclusivity trials, would think that, in fact, that's potentially unrelated to the drug and related to the disease. And so none of that data emerged out of this. What it emerged out of is a review of the exclusivity trials themselves.

And at some point, I think it would be worth just discussing as a general topic, apart from the--you know, as we've done on individual agent can we do better than this system and what would that look like. And I'm not sure what the answer would be in terms of that, but I'm struck--my impression is that we wouldn't have seen the signal that we saw that led to the past two-day meeting using this system. And the only way that came up was with the request to exclusivity studies.

DR. IYASU: Yes, well, let me make a comment. As you recall, since you've been involved in this committee a couple of years, we did a report on suicidal ideation and also suicidal behavior associated with drug products like

Citalopram and Paxil in the past. Now, we know the limitations of the system in terms of trying to get a handle on what the rates are or, you know, the estimates of the risk on this adverse event. Nevertheless, I think the AERS system, the best it can do is that it can sort of identify some adverse events that may not have been detected during the clinical trial, but sometimes it's also possible that if you see it in the clinical trial setting and you see it also in the one-year post-exclusivity period, then it sort of raises a question.

So, actually, I want to go back to what happened early last year when we were talking about Paxil. The discussion of the clinical trial data was done in conjunction with the adverse event report, so it was supportive in the sense of us--you know, mandating us to look more carefully at the clinical trial data because we were also seeing these reports in the Adverse Event Reporting System.

So I would say that the AERS system cannot

give you an estimate, but it can just focus you or even help you look more closely at clinical trial data if you do see these kind of events.

DR. MURPHY: Skip, I think what you're bringing up is a really important question, and actually, I was going to say this at the end of the meeting, but after we do maybe one more meeting with the new committee with this process, you will see we have already internally decided--and Dr. Lumpkin is now my new boss, and we want to internally review, including, you know, Office of Drug Safety, New Drugs, and other Centers, have an internal review of how to enhance the way we go about the safety reporting, because it's very clear to us that Congress wants us to be able to make valid reviews, if you will. We're all telling you there are problems with this system and we all know, so how can we enhance it? And I think the prior committee has seen that we've gone from just reporting AERS and what's in the label, to going back to the actual original clinical trials, looking at signals in those clinical trials and

trying to tell you what was seen then, what's seen in AERS. So we really do agree that we need to try to develop the most robust way of doing this.

Now, having sort of laid bare the fact that we all think this is not the best system and we want to make this a useful process, I will tell you that just having the process has an impact that you don't see. Okay? You know, having been mandated and going to a division and saying this product is coming up for review and we need--it means the divisions, ODS, everybody has to go back and look at this material. And as Dr. Iyasu was saying, Paxil was a--I think we mentioned to you, we delayed actually presenting that because of all of the activity that was going on. And when we looked at the AERS system, we saw some actual concerning things. Now, we couldn't make any attribution, but compared to the other products--and you have to do all those--you know, the other products weren't used as much, et cetera, there still were some things that were concerning.

So I think we feel that the process, even

as it is right now, has served some useful purposes, but that clearly we would like to enrich it and make it more robust and make it more scientifically useful for the committee to understand, because, otherwise, what we're always doing is putting pieces--you know, we're taking pieces of data and trying to make sense out of these pieces of data.

So the intent is that we will be coming back to you, and as I said, we'll see, you know, how the next meeting or so goes, give the new committee an opportunity to see this and provide us additional--and probably come to you as a complete subject unto itself, a topic for the committee, how to better do this process.

DR. NELSON: And just to--my comments are meant to be critical in the positive sense. The progress since when I remember first hearing some of this data two years ago has been phenomenal in terms of what's been able to be accomplished with all the warts and pimples of the existing data. So just to say that.

DR. IYASU: Thank you. I appreciate the comments, and we're always open to suggestions to make it even better and make it more useful.

DR. CHESNEY: I think Dr. O'Fallon and then Dr. Ebert. No? Dr. Ebert.

DR. EBERT: This is somewhat related, and I wonder whether the agency has considered this as well. But a lot of what you've focused on have been, of course, adverse events that have happened. But I'm wondering whether there is also the opportunity to screen for medication errors that occur and whether that entire--it may be a slightly different database, whether that's through IMSP, for example, and whether there may be systematic errors that occur in treatment of pediatric patients as opposed to adult patients, whether it's product selection or selecting the wrong product because it looks similar to another substance, for example.

But it seems that there's obviously been an increasing public outcry for making sure that our medical practices are also safe in addition to

these adverse effects that occur.

DR. IYASU: I think that's an important point. Again, AERS has limitations in that area, but, nevertheless, I recall in one of the presentations we had an issue with medication error involving two products, one was Zoloft and Zyrtec, and that came out loud and clear, I think, in the adverse event review, and there may be others also that may be picked up. Yes, that's an important issue.

DR. CHESNEY: Dr. Maldonado?

DR. MALDONADO: Yes, I have a couple of questions of process or actually what you said that one of your list of five items there was unique and unexpected pediatric AEs, and I just kind of went through some of the presentations. Is that data going to be presented in a way that we can actually see if there is excess pediatric risk in the use of these drugs, an excess compared to adults? Typically most of these drugs that are used in adults tend to advertise more than in children, so seeing a list of adverse events in children, maybe

because I'm used to seeing it, without the context of knowing is this an excess risk? Are children suffering an excess risk of X adverse event? Or is this just the background that you see in the use of the drug? That's one thing. And I haven't seen that in previous presentations.

And so I come out of the meetings, okay, yes, I saw several adverse events and some of them very horrible adverse events, but it doesn't give me a sense is this something that is a red flag in pediatrics that needs to be looked at more closely? That's probably why Dr. Santana asked for the adult data on SSRIs yesterday, and not so much to look at the adult data but is an excess risk there in children?

And the other thing, in your last slide you said keep in mind the off-label use of fluticasone. What exactly is it you want us to focus on when the presentations come so we're alert to that?

DR. IYASU: Are you talking about the question?

DR. MALDONADO: Pardon me?

DR. IYASU: Are you talking about the question?

DR. MALDONADO: Yes, the last slide. I just don't know what you want us to focus on.

DR. IYASU: I think the focus would be for you to consider the presentations regarding these drug products, and there will be a series of them, and then to get your input as to whether there is any additional labeling concern or information that you would like to include in the label, concern about the drugs as--the use of the drugs as labeled currently. So there is a concern about that. Of course, you have the label that is included. So it's as labeled now, they have been used in different ways, and is there any concern regarding that.

DR. MURPHY: Sam, they're going to present what they think the adverse event, if you will, is, what they've done to deal with it, what's in the label now, and does the committee think that's adequate. So it's really--you're right. You don't

have any information to answer that question. They're just trying to show you where they're going with the information they're going to present.

DR. IYASU: The context for that question will be clearer, I guess, once the presentations are done. But to go back to your first question about the unexpected--or regarding whether adverse events are occurring in excess in pediatrics as opposed to adults, I think that's an important question, and we haven't really done this for the products. We do a top-line review for the one-year period, and then most of the review has focused on whether the same adverse events have also been reported in adults. And we do sort of that kind of comparison based on how frequently the adverse event terms, as we call them, are reported.

When there is an issue that may be considered to be critical, then we would like to do sort of additional cultivations trying to see what the background rates are, and then also look at what the reporting rates are. We haven't done that except, I guess, for SSRIs. But for other

products, that's something that can be done, but, you know, you must know that there are a lot of caveats in trying to come up with a reporting rate or relative reporting rate for these drug products. But when there is a need to do that, we will actually do that.

DR. CHESNEY: Dr. Nelson has a question for you.

DR. NELSON: Actually, just a comment on that. Knowing the deficiencies of the system for being able to get the denominator, it's not clear to me that we necessarily need to look at the ADER system in adults and compare them, and you're sort of comparing information where you don't know the denominator in either case.

If you're comparing it to the data that obtain in clinical trials and look beyond just the pediatric data in clinical trials to the adult data in clinical trials and look at it in that context and see if there's anything, it's different as a signal for adults, probably that would be useful data because then you can actually establish

frequency for adults because we have a hard time establishing frequency in pediatrics using this data, which is the main problem with it.

So I wouldn't encourage you to try and do the thing that we can't do in kids in adults, too, but if the comparison is made with clinical trials where you can have that denominator, then that might--then I think that would probably be useful information.

DR. MALDONADO: I was referring actually--I've seen some drugs presented that I'm very familiar with, and what I've seen here presented, it's not very dissimilar to what I see outside this room, meaning that the same adverse events actually in absolute numbers, much larger in adults. So my question when I see those presentations here, is this a signal in pediatrics? Should it be worried to--and I'm not saying that we should look at the data. I mean, I think they do a good, a much better job looking at the data. That's what they do for life. But it's to identify for us excess risks, because those are the ones that you really

have--and I know it's difficult. I know it's difficult. But just looking at that list without the context, it leaves me like, yes, I'm not surprised that this is happening, this is happening in adults 10 times more or 20 times more.

DR. IYASU: I think you make an important point there, and we just have to live with the limitations of the data. What we can do, when it's an important issue, serious adverse event, we can go out on a limb and go to other databases like Claims database, which has its own set of limitations and caveats. So there are many avenues that you can go, but reporting rates or relative reporting rates are the best that we can do with this limited data set. We have refrained from doing that because of the limitations in terms of defining the actual numerator that you use, and also the denominator, especially for pediatric. So we may--we're concerned about sending the wrong signal as to the relative safety of certain drugs if we don't have--if we're dealing with uncertain denominators and uncertain numerators. So that's

where, I think, the problem is in trying to assess it.

So what we've done is if there is really an issue, then our best resource is really the clinical trial data. And what we've done is the initial sets of presentations that we've done for adverse events for these drugs did not include a review of what was actually in the clinical trials done for exclusivity. Now all our reviews include summaries of the exclusivity trials and what kind of safety signal this might have resulted that may be similar or been supported by the adverse event reports.

So we're trying to strike a balance here and trying to give you the best information that we have with all the limitations for interpretation. So I can't say anything more than that. If there are other suggestions from the committee, we'll be very glad to consider them to improve the system.

Thank you.

DR. CHESNEY: I think it also doesn't address the issue of the drugs that didn't go

through exclusivity. But I think in your spare time, if you could develop a national database that would capture this inform for us.

[Laughter.]

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: This brings us back to the problem--clinical trials provides the very best data we have, no question about it. You know, I'm a lover of clinical trials. But there's all those comorbidities that are excluded that are encountered, and a good chunk of the patient population are excluded often from these clinical trials. And so the question is: If there are a lot of adverse events being encountered by kids being treated with these things but they're not in clinical trials because they keep getting ruled out due to the exclusion criteria, does the adverse events--the MedWatch, does that capture those? If the parents are screaming, do those--like those people that were the public presenters on Monday, are their cases ending up in MedWatch?

DR. IYASU: Well, consumers also, you

know, send their reports through the MedWatch program. Health professionals do. But as I said before, 80 percent--or more than 80 percent or 90 percent of the reports are actually from manufacturers. Some of them may actually have been reported directly to manufacturers from health professionals, and then they are transferred to us.

The extent of the reports of adverse events or experiences of adverse events by patients directly is variable. It's small, actually. Probably it's very underreported.

DR. O'FALLON: Yes.

DR. IYASU: So we really don't have a way of capturing that through a passive system such as AERS, unless you go and do an active surveillance system, which is a resource issue.

DR. O'FALLON: Yes.

DR. CHESNEY: I think unless there are any other pressing questions--we're about a half-hour behind, so maybe we need to move ahead. Dr. Iyasu is going to introduce our next speaker.

DR. IYASU: Thank you. Our first speaker

for this section of adverse events is Dr. Hari Sachs. Hari is a professor of pediatrics with over 15 years of experience in private practice. She also served on the FDA Non-Prescription Drug Advisory Committee and is one of the FDA liaisons to the American Academy of Pediatrics Committee on Drugs. She will be presenting the adverse events for ofloxacin and alendronate.

Dr. Sachs?

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DR. SACHS: Thanks again for that kind introduction. Forgive me, I'm a little mechanically challenged, so if I screw up this presentation, at least the mechanics of it, bear with me.

I'll be discussing the adverse events for ofloxacin, trade name Ocuflox, which is an ophthalmic anti-infective that was approved in July 1993 for the treatment of conjunctivitis and corneal ulcers due to susceptible bacteria in both children and adults over one year of age. Depending on the condition, one to two drops of ofloxacin applied to the eye at frequent intervals.

The exclusivity was granted in March 2003 based on studies of neonatal conjunctivitis, although ofloxacin is not approved for that purpose.

As you can see from these statistics, millions of prescriptions for ofloxacin were written for both adults and children during the one-year exclusivity period. Pediatric patients accounted for almost one-third of these prescriptions. And, in fact, pediatricians prescribe almost as much ofloxacin as ophthalmologists, and not surprisingly, the most common indication is conjunctivitis.

Now I'll look briefly at the studies performed for exclusivity, and as you can see, they are posted on the Web.

The pivotal study was a one-week, active control trial which compared ofloxacin and trimethoprim sulfate treatment of conjunctivitis in infants less than one month of age. The clinical cure was based both on resolution of discharge and erythema by (?) lamp exam and microbiology cure. The safety of ofloxacin is comparable to that which

is seen in older patients in previous trials. But although the clinical cure rate for ofloxacin exceeded the active control, neither of the two drugs exceeded the historical control, and, therefore, the study was--it was deemed that this was not an approvable indication.

Note that the vehicle that's used that's the historical control does contain benzyl chromium, which has antibacterial properties.

The submitted data from this trial doesn't really allow us to figure out why the cure rate was low, why this study didn't seem to work. But potentially there are factors related to the design or conduct of the trial, the bacteriology of neonatal conjunctivitis, or perhaps the time course of it, or maybe a combination of all these factors.

In discussing the relevant safety labeling, I'm going to highlight information that's either pertinent to pediatrics or the adverse events. Ofloxacin is a Pregnancy Category C drug since there are no studies in pregnant women and there are some effects on animals. It is

potentially excreted in breast milk. Under the Pediatric Use section in precautions, there's a statement that although the oral form of ofloxacin has been associated with arthropathy in juvenile animals, there is not an association for the topical form.

There is a warning about allergic reactions, including anaphylaxis, which details a case report of Stevens-Johnson syndrome from the topical preparation. Most adverse reactions to ofloxacin, however, are really mild and include ocular burning or discomfort and, very rarely, visual changes such as photophobia or blurriness or systemic symptoms may occur.

Now that you're familiar with the label, let's look at the adverse events. As you can see, there really are very few reported adverse events for ofloxacin in all ages. And during the one-year post-exclusivity period, there were only three reports--or three events, actually, all unlabeled, two of which occurred in one adult and one that occurred in a pediatric patient.

The pediatric event was a foreign report that is also found in the literature of corneal deposits in a 6-year-old who was receiving the ointment. That's not available in the U.S. And, in general, these types of corneal deposits actually resolved by themselves and are thought to be benign. This patient was actually treated with scraping fairly early in the course. The natural history actually is that it should have resolved.

With such few events, we really can't draw a meaningful conclusion, and while this completes the one-year post-exclusivity adverse event monitoring, as mandated, we will continue our routine monitoring of adverse events for this drug.

Are there any questions?

DR. NELSON: Just to repeat what I think I--you're unable to tell the ages of the pediatric use. You can't tell how old the conjunctivitis prescriptions were? In other words, is it being used on-label above one year of age, or is there any off-label use--

DR. SACHS: Most of the use was on-label.

There's one database that captured some of the use in kids under two, but it didn't separate out which were under one. So it didn't help. It is approximately 20 percent of the pediatric use for that, the lower age group.

DR. CHESNEY: Thank you very much.

x DR. SACHS: Switching gears from one system to another, I will now discuss the adverse events that occurred during the post exclusivity period for alendronate.

Alendronate, or trade name Fosamax, is a biphosphonate which inhibits bone resorption by osteoclast, and it was originally approved in September 1995 for the treatment of osteoporosis in adult women. Pediatric exclusivity was granted in April 2003 based on studies of children with osteogenesis imperfecta.

Currently, alendronate is approved only in adults, and it's for the treatment of osteoporosis for both men and women, its prevention in women, and for Paget's disease. The dosage varies from indication, and there are really no pediatric

indications.

As you can see from these numbers, although Fosamax is widely prescribed in the U.S. for adults, and the use is increasing, the use in pediatrics is really minimal. There's like 10,000 prescriptions in pediatrics compared to 22 million for adults. Alendronate is primarily used in the outpatient setting with the lion's share of prescriptions from internists, OB-GYNs, and family practitioners. Pediatricians write very few of these.

Osteoporosis and osteopenia were the primary indications for therapy in adults, but in pediatrics alendronate is used off-label for treatment of osteoporosis and osteopenia either due to underlying disease, such as renal or connective tissue disease, or for its therapy, glucocorticoid therapy, for example,, fibrous dysplasia, and as you will see, osteogenesis imperfecta.

I'll briefly discuss the results of the studies that were performed for exclusivity.

Both pharmacokinetic and safety and

efficacy and safety studies were performed to evaluate the treatment of severe osteogenesis imperfects, or OI, in pediatric patients ages 4 to 18. The PK studies found that the oral bioavailability of alendronate relative to the IV dose was really similar in both children and adults. Exclusivity was granted based on submission of the 12-month analysis of this trial in pediatric patients with OI, and both doses that were used in the trial did significantly increase lumbar spine bone marrow density, which was the primary endpoint. But, unfortunately, a key secondary endpoint was not reached, and that was actually the occurrence of fractures either by report or by x-ray.

The adverse events in the one-year analysis appear comparable to those seen in adults, and it's hopeful that this trial--there's going to be more data coming in on a one-year extension of this trial.

Once again, I'd like to highlight the relevant safety labeling for pediatric patients.

Alendronate is considered a Pregnancy Category C drug, with animal studies that have shown maternal hypocalcemia that sometimes leads to early delivery, and although there's no human data, theoretically there can be an effect on the fetal skeleton.

Due to significant gastrointestinal irritation, alendronate is contraindicated in patients who have a risk of esophageal emptying--excuse me, have a delay in esophageal emptying or risk of aspiration or cannot stand upright. And patients with hypocalcemia or allergy are told not to take the drug. Esophageal perforation, including ulcerations or erosions, are also described in the warning section of the label.

Precautions include the recommendation to monitor calcium and vitamin D status. And gastrointestinal symptoms, such as abdominal pain or nausea, musculoskeletal pain, headache, dizziness, and taste perversion are the more common side effects that are seen.

Now, since alendronate approval,

paralleling the relatively small percent of pediatric use, pediatric adverse events really represent only a very small percent of adverse events. There were 17 total reports for pediatrics out of 18,000 total reports. And this is kind of indicated in the post exclusivity period as well, with only four pediatric case reports that were unduplicated. And there were no deaths.

The four reports include two cases of hepatocellular injury, one patient that suffered a drug-drug interaction potentially, and one infant that had hypocalcemia and prematurity.

Hepatotoxicity was noted in two children that were treated for steroid-induced osteoporosis, and the details of their cases are reported on this slide. But, briefly, liver dysfunction was temporarily associated with the onset of alendronate therapy and resolved after its discontinuation and treatment with pulse steroids in both patients. One patient did have underlying liver dysfunction, and the other patient was on methotrexate.

The drug interaction occurred in a 7-year-old with JRA who was taking cyclosporine, and after starting alendronate, the cyclosporine levels decreased, and his disease flared. Once the alendronate was stopped, the cyclosporine levels returned to normal. There was some fluctuation in baseline levels, so the exact interaction is unclear--I mean baseline levels of the cyclosporine, that is, before the alendronate was started.

The last case was the prenatal exposure which describes hypocalcemia, hypocortisolism, and prematurity in a male infant that was born to a woman with multiple medical problems, including gestational diabetes, and who was on multiple medicines. Hypocalcemia is known to occur in premature infants, infants of diabetic mothers, and several of these therapies, as well as potentially with alendronate.

So, in conclusion, only a handful of adverse events were noted. Most did have confounders or insufficient information to ascribe

causality. We did look at a preliminary analysis of the adult hepatic events, and that does not seem to raise any concerns. And this will complete the mandated reporting for alendronate from BPCA, but we will continue its routine monitoring.

Are there any questions?

DR. CHESNEY: Dr. Maldonado, and then Dr. Nelson.

DR. MALDONADO: I observed that in the ofloxacin you had only one adverse event, and it was a different drug product, it was not the same drug product in the United States?

DR. SACHS: Right. Well, it's the ointment form as opposed to we just have drops.

DR. MALDONADO: So it's a different drug product.

DR. SACHS: Correct.

DR. MALDONADO: And in Fosamax, also the four reports were ex-U.S.

DR. SACHS: That's correct. They were foreign reports.

DR. MALDONADO: Do you know if it's the

same drug product, or is there a possibility that it is a different drug product?

DR. SACHS: I believe that it's the same drug product.

DR. MALDONADO: And the reason I ask, for those who are not familiar, you see internationally the same names, and sometimes they are different products actually, because the FDA approves drug products, not drugs or--and sometimes there are different components in the drug product. So when you include them, actually that's good that you highlighted that, because that may be relevant to the adverse events.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: Just a question about labeling, but not in the safety and efficacy component. I don't understand, if, in fact, there's been a pharmacokinetic study, why we would say that the pharmacokinetics have not been investigated in patients less than 18 years of age. I mean, that's what the label says. Wouldn't we normally include some pharmacokinetic data even if

we don't think safety and efficacy has been established?

DR. MURPHY: No.

DR. NELSON: Why?

DR. MURPHY: Because you're giving it an implied approval. You're giving the dosing. Now, if the--not always.

DR. NELSON: Well, we can--

DR. MURPHY: Let me--you know, that's a whole big discussion, and you heard we have this tension between trying to inform and not providing a marketing freebie at the same time. So if that pharmacokinetic study was done and found that there was, you know, something very different going on or some concern, then we could say on a dosing--I'm talking about past. I'm talking about prior practice, okay? So whether that's all going to change--you know, it's good to provide you feedback on this. I just wanted to say that in the past one of the concerns that has been expressed has been any information you put in the label about pediatrics--I'm just starting from the big global

concern--depending on what it is, if it's not a safety, you know, warning, in essence provides a de facto approval and/or an ability of the company to market it.

As an example, they could go out and say, well, look, FDA put this information in the label about how to use it in kids. So there is that balance of trying to make sure that it's clear if we put information in, in what context that information is put in the label.

Now, I mean, please proceed to say you think we should have put it in the label; we're interested in hearing that sort of stuff. But I'm just trying to provide why we routinely wouldn't put information that we obtain into the label.

DR. NELSON: Just a quick response. I was heartened to hear from Bob Temple yesterday that that position was being readdressed. I previously, until your comment, wouldn't have applied it to just basically the pharmacokinetic information. But I'll also point out that most people, myself included, get my information from personal device-

based systems, which do include dosing data. And, in fact, one of those two systems I have on my Palm actually included depression as an indication for an unlabeled use.

So I appreciate the concern about encouraging it, but I actually think adding more information might, in fact, discourage it if there was an emphasis of making sure that information was, in fact, accurate and then transmitted accurately to clinicians. I know that's a whole broader discussion, but--

DR. MURPHY: I think we need to hear that. I mean, that's what this committee is here for. You're looking at the pediatric perspective on this, and there has always been this tension. And I think I've told this committee before, there are those of us who think we are mandated in some ways to put some of this information in the label. There have been others in the agency who have been very concerned about doing that.

I think what you heard yesterday was a very different approach that's being considered.

So we do want to hear these comments.

DR. CHESNEY: Dr. Maldonado, then Dr. Fant.

DR. MALDONADO: I'm just going to give you a perspective, and Dr. Murphy is right, people may misuse the information. I'm not saying that that wouldn't happen. But, for example, the drugs that are being used off-label--and we know--and I'll just give you the perspective of one that I'm working--it's a company, and we rarely have the PK data. And we now found out, although we believe that the dose being used off-label was the correct dose, and that's the dose that we use in the PK, we found out that that's incorrect, that children are being underdosed. This is an antimicrobial.

The clinical studies are ongoing, and they may be ready in five years, by the way, because of the long-term follow-up that we need to do. In the meantime, people are using off-label this drug incorrectly. And you're in the bind that you cannot communicate that because it may be perceived as, you know, promotion. But you want to

communicate it. It's difficult. I know exactly the concern that the FDA has because it can be misused. But at the same time, not conveying it, it allows people to continue using the drug incorrectly.

DR. NELSON: Can't your solution be--I assume there's some academic investigators potentially involved at study sites, letting them release at least the PK data in a publication? Or does that also violate--I mean, here it sounds like you might even have a moral obligation to put out that data.

DR. NELSON: Yes, the data has actually been published in a poster format so people who are more sophisticated in the area of infectious diseases already know that that's incorrect. And that's as far as we've gone.

DR. MURPHY: But I think that this is a perfect example of the quandary, because as all of you know--and you heard yesterday--we have a history of putting things in the label that nobody ever finds anything about the information. I mean,

that's just the way life is. And with our health care system the way it is right now, it's actually getting worse, one could say, I think, as far as physicians having time to access some of this information in a timely manner.

But I would say, you know, if I were in the Anti-Infectives Division and the company came to me and said, oh, we've got this information, we want you to put it in the label, but we're not ready to submit our application yet to show you whether it's safe or efficacious, you can see what the problem is.

DR. CHESNEY: Dr. Fant?

DR. FANT: One small point for completeness related to the case of neonatal hypocalcemia. You highlighted with an asterisk the drugs known to be associated with hypocalcemia, but it may be worth also putting an asterisk and highlighting the condition of diabetes itself in addition to the prematurity.

DR. SACHS: Yes, I mentioned that.

DR. FANT: Oh, okay.

DR. SACHS: I just put the medications, but yes, oh, yes.

Behind these presentations, actually, are a group of folks at ODS and in the divisions that contributed to the report, and I just want to kind of publicly acknowledge them as well: Jennie Change, Renan Bonnel, Mark Avigan, Wiley Chambers, Gianna Rigoni, Judy Shaffer, and Michael Evans. So there's actually a lot of people that go into these presentations that you don't see.

I would now like to introduce Dr. Susan McCune, who is a neonatologist, whose previous experience has included academic neonatal practice at Johns Hopkins and Children's National Medical Center. She recently received her master's degree in education and has worked on computer-based educational models for pediatrics. She will be presenting the adverse events for fludarabine.

On a personal note, it's a pleasure for me to be working with her again because she was, I think, my chief resident when I was a resident at Children's. Things go full circle.

DR. McCUNE: Thank you, Hari.

It was an honor to work with Hari as a resident, and it's an honor and a privilege 20 years later to work with her again at the FDA.

As Dr. Sachs said, I'm going to discuss the one-year post-exclusivity report for the adverse events for fludarabine.

In terms of background information, fludarabine, or trade name Fludara, is a synthetic adenine nucleoside analog that primarily acts through inhibition of DNA synthesis. It is produced by Berlex Laboratories. Its indication in adults is for the treatment of adult patients with unresponsive B-cell chronic lymphocytic leukemia. Of note, there are no pediatric indications that are approved for this drug. The original marketing approval date was April 18, 1991, and pediatric exclusivity was granted on April 3, 2003.

I want to stop for a moment and talk to you a little bit about the background of oncology and pediatric drugs at the FDA, and I think this gets a little bit to some of the questions that

you've been asking about because oncology drugs are a little bit different from some of the other drugs.

There has been a special initiative at the FDA to increase pediatric drug labeling for oncology drugs and to prioritize the availability of new oncologic agents to pediatric patients. To achieve this goal, three items that I'd like to point out for your attention:

The first is the draft guidance for industry that's entitled "Pediatric Oncology Studies in Response to a Written Request" that was published in June of 2000. The guidance is part of this initiative to generate new knowledge to assist practitioners and to provide early access to emerging new drugs.

In addition, the Best Pharmaceuticals for Children Act that was signed into law on January 4, 2002, established the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee and prioritized new and emerging therapeutic alternatives that could be available to treat pediatric patients with

cancer.

Another report entitled "Patient Access to New Therapeutic Agents for Pediatric Cancer," which was published in December 2003 and was a report to Congress, was a report that identified areas in pediatric drug development that could be improved to facilitate access to new agents.

Now I'm going to focus a little bit on the trials that were done for exclusivity for fludarabine.

Exclusivity was based on data that was submitted from two previously published COG trials: CCG-097 and CCG-0895. CCG-097 was a Phase I dose-finding and PK study of a loading bolus followed by a continuous infusion of fludarabine in patients with acute non-lymphocytic leukemia, acute lymphocytic leukemia, and solid tumors. CCG-0895 was a Phase I/II dose-finding, PK, and pharmacodynamic study of a loading bolus followed by continuous infusion of fludarabine, then followed by a loading bolus and continuous infusion of Ara-C in children with previously treated acute

leukemias.

I'm going to talk a little bit in detail about the first trial, which was CCG-097. There were two groups of patients, first those with solid tumors and those with the acute leukemias. The patients with the solid tumors reached a maximum tolerated dose because of dose-limiting toxicities that were hematologic--in other words, myelosuppression. The patients with the acute leukemia, the goal was marrow ablation, so their maximum tolerate dose was not reached based on this toxicity--toxicity associated with the solid tumors, but their dose was limited by the concern for potential CNS toxicity that had been seen with adults. Of note in this trial, there was one complete and three partial remissions in 26 evaluable children with ALL.

The pediatric adverse events that were noted in this trial and are included in the label are marrow suppression, especially of platelets, fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. No peripheral neuropathy

or pulmonary hypersensitivity was seen in these trials.

The second trial, CCG-0895, which I had previously told you was a sequential administration of fludarabine followed by Ara-C, was undertaken in 31 patients either with ALL or AML. Of note, in the patients with ALL there was a 33-percent complete or partial response, and in those patients with AML, there was a 50-percent complete or partial response. This study was not able to provide data on the efficacy of fludarabine alone, but did provide efficacy and safety data for the combination.

I'd like to just point out--let me see if I can do it here--that this information from the first trial, CCG-097, has been included in the label as of October 2003. There are two parts of the label that have been changed. The first is the clinical pharmacology in special populations pediatric patients, which highlights that steady-state conditions were reached early. And then in the precautions section, pediatric use, this is a

description of that trial that I just told you about, followed by the treatment toxicity that I also pointed out to you.

In terms of drug use trends in the outpatient setting or sales of fludarabine, this is considerably different from what Dr. Sachs presented to you with her millions of prescriptions. Approximately 280,000 vials only of fludarabine were sold in the U.S. annually from May 2001 through April 2004, with no significant increase seen after exclusivity. And as Dr. Iyasu pointed out to you, this particular database is one that does not divide it up in terms of pediatric and adult use. Just as you would expect, fludarabine was primarily sold to clinics and non-federal hospitals during the 12-month post-exclusivity period.

In terms of drug use trends in the inpatient setting, where we do have some pediatric data, Premier data showed us that pediatric use accounted for 3 percent of discharges between 2002 and 2003 in which fludarabine was billed. And CHCA

data demonstrated that from October 2002 through September 2003, there were 95 discharges associated with fludarabine, which were essentially unchanged from the previous year.

Now I'm going to switch gears and talk to you about the adverse event reports for fludarabine in the one-year post-exclusivity period from April 2003 to May 2004.

The total number of reports for all ages were 300, with approximately a third of them occurring in the United States. As expected, almost all of them were serious, and over a third of them involved deaths.

In terms of the pediatric reports, all of them were serious. There were ten unduplicated pediatric reports, only one of which was in the United States, and the outcomes for three were death, and seven were hospitalized, one which suffered continuing sequelae.

Of those ten pediatric patients, the recorded use was for six preconditioning for bone marrow or stem cell transplant; for three, AML

relapse; and for one, JMML with splenectomy prior to bone marrow transplant. The age for these reports was predominantly in the 2 to 5 age range with six reports, one each in the one month to less than 2 years, and the 6 to 11 year age ranges, and two in the adolescent population.

Dr. Maldonado, this may get to your question earlier. These are all the adverse event reports for fludarabine in the one-year post-exclusivity period, both adults and pediatric patients. As you can see, there are a significant number of adverse events. Those that are underlined are actually unlabeled events, including increased bilirubin, abdominal pain, and then three related to either drug ineffective or disease recurrence. In the pediatric population, the only unlabeled event was abdominal pain.

I'm now going to give you a brief discussion of each of the ten pediatric patients followed by a summary of their categories and a comparison with the adult information in the label.

There were three deaths. The first was a

four-year-old with ALL who received fludarabine for preconditioning for stem cell transplant. The day after transplant, she developed fever, shock, and multi-organ failure. This was one of the cases that also reported abdominal pain.

An eight-year-old with ALL who received irradiation, fludarabine, and cyclosporine followed by stem cell transplant, who six days after transplant became febrile with a rash, generalized edema, tachycardia, abdominal pain, and cardiac arrest.

Of note, one of the later cases is a cardiac tamponade patient. We don't have additional information, but the tachycardia to over 200 along with the edema could be possibly concerning for that as well. But there is no additional information.

And the third and final death is a 13-year-old with bone sarcoma of the rib who received fludarabine as preconditioning for stem cell transplant and then developed carcinomatous pleurisy and died of disease progression.

In terms of the seven hospitalizations, there was an 18-month-old with hepatic veno-occlusive disease after bone marrow transplant for beta-thalassemia. There was a two-year-old with relapsed AML who developed photophobia on the FLAG study, which is fludarabine, cytarabine, and granulocyte colony stimulating factor. There was no photophobia noted on rechallenge.

And then I want to highlight an additional visual disturbance in a three-year-old with relapsed AML also on the FLAG study that developed bilateral blindness, which resolved leaving some degree of blindness, and that's the sequelae that I spoke of.

There was a four-year-old with AML relapse who developed encephalopathy and recovered.

The only United States case is a four-year-old with JMML with splenectomy in preparation for bone marrow transplant, who developed fever and pneumonia.

There was a five-year-old with AML after bone marrow transplant who developed aphasia,

vigilance disturbance, and non-specific encephalopathy. This is a foreign report. It's not clear whether vigilance disturbance is a disturbance of state associated with encephalopathy or could potentially also be visual disturbance, although most likely just a disturbance associated with the encephalopathy.

And then, as I previously mentioned, a 13-year-old with bone marrow transplant for aplastic anemia who developed cardiac tamponade and cardiac failure four days after transplant, who recovered with diuretics and pressors.

So, in summary, there were ten clinically significant pediatric adverse events, and if you break them down into four categories, there was cardiac failure in two, cardiac tamponade in one, and cardiac arrest in two. This is labeled for adults for edema and pericardial effusion. The abdominal pain that I pointed out to you before that was not labeled in adults, it is labeled for nausea, vomiting, anorexia, diarrhea, stomatitis, and GI bleeding in adults. And as I pointed out,

the two patients that had abdominal pain in the pediatric age range were those with multi-organ failure and death.

There were two pediatric patients with blindness and optic nerve disorder, and this label, as I will show you in a moment, is labeled for visual disturbance and blindness in adults. And encephalopathy is also labeled in adults.

Just to give you an idea in terms of whether this is a different signal from what's seen in adults, I showed you the most common adverse events in terms of those that were more than 20. In this same period of time, all of these events were reported in adults in the range of three to five adult reports.

And I just wanted to show you, this is the boxed warning for Fludara, and this gets at a couple of issues that were discussed actually yesterday. This drug should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. In addition, it is labeled in the boxed warning

that it is associated with severe neurologic effects, including blindness, coma, and death. Also labeled here are fatal autoimmune hemolytic anemia, and down here a warning about the combination of use with pentostatin and fatal pulmonary toxicity.

So, in summary, there are labeled and unlabeled adverse events for fludarabine that have been reported. There are a number of pediatric adverse events that were reported in the post-exclusivity period that were not recognized in the clinical trials that were done for exclusivity. These adverse events, however, have been labeled for adults. These serious adverse events include encephalopathy, blindness and other visual disturbances, and cardiac tamponade and failure. These patients tend to be on very complicated, pre-transplant regimens that involve multiple medications and immunosuppression. I just want to note that this completes the one-year post-exclusive adverse event monitoring as mandated by BPCA. But the FDA will continue its routine

monitoring of these adverse events for this drug.

Any questions?

DR. CHESNEY: Thank you very much.

Comments, questions? We need Dr. Santana, who is in Oslo.

Any other comments? Dr. Murphy, are there any--

DR. MURPHY: I think, you know, this is just one of the things we'll be looking at in the future when we review these and we don't think we see anything going on. How much information do you want? Do you want us to present it? Do you want us to send it to you beforehand? When we say we are going to no longer do--when we say this completes the exclusivity reporting, it means that this process will no longer occur, and that we are basically telling you that we think that that appears to be an appropriate outcome, unless you tell us something differently than that. We'll now go back to the usual process of just the Office of Drug Safety doing their reviews and we won't be reporting this to you.

So I did want to make that clear to the new committee members. That's what that means when we say that. We don't have any specific questions for this product.

DR. CHESNEY: Dr. Fant?

DR. FANT: Yes, just a question. Out of curiosity, how did the signals that emerged from the use of this drug, given the complex nature of the disease and the drug regimens that these kids are on, compare with the signals that emerged in previous reports for some of the other drugs?

DR. McCUNE: For the other oncologic agents or other drugs in general?

DR. FANT: Well, the other oncologic agents in these types of patients. Any way to sort of get a sense of whether there's something unique about these signals versus the others?

DR. McCUNE: I actually reviewed two oncologic drugs the last time we presented for this committee, and I think the process that we're really looking for is what you all have pointed out: Are there substantial differences from the

adult population? Are there substantial differences from what's in the label that should be potentially added to the label? Although that's very difficult given all the confound--the small numbers of patients and the confounding. And I think that it becomes very difficult because most of these drugs are not used except in patients who have recurrent disease, so they have disease progression. They're also on multiple other drugs and multiple other regimens.

So it can be difficult to pull out a signal. That's why we very carefully look at each one of these adverse event reports to try to see if maybe there's something more there or if there's a relationship that does not show up in the label for the adults. And so far, with the three drugs that we've reviewed in the last year, I haven't seen a substantial difference. They're very low numbers of usage for the drugs in general in the population, 200,000 versus millions of prescriptions. And then the pediatric use in that is very low. Because of that low number, that's

why there's been this initiative to try to get drug labeling for oncologic drugs because, otherwise, we wouldn't have the data to be able to do labeling or to be able to get these drugs to the population quickly.

DR. CHESNEY: Dr. Ebert, and then Dr. Nelson.

DR. EBERT: When you identify adverse events that have not been seen previously in pediatrics but have been seen in adults and are in the labeling, is the implication that the labeling does not need to be modified or that it does need to be modified?

DR. McCUNE: In general, when it's been stated in the label for adults, that's considered labeling. If there were something where there was a substantial signal without the confounding variables, that would be something that could be discussed. But, in general, unless there's a very strong signal that is different from what's seen in the adults, the label is considered to be adequate.

DR. CHESNEY: Thank you. I had that same

question, so thank you.

Dr. Nelson?

DR. NELSON: Just a comment before leading up to a question. I noticed the significant amount of pharmacological information in the label, as you pointed out, in terms of pharmacokinetics, and I speculate I know part of my comfort level with the use of these drugs is the fact that in the United States 90 percent of the children are treated on protocol, and the chances of this being used off-label are exceedingly low. Is that different in Europe? Is this either labeled or do they have--I mean, I'm just wondering why this seems to be used more frequently. Maybe, you know, in that case, I assume it's not labeled for a pediatric indication in Europe, but they must not have as much of a control over what happens to where someone's obviously using it for bone marrow transplant protocols.

DR. McCUNE: I don't know the answer about labeling in Europe.

DR. MURPHY: That's one place we haven't

looked. But I do think that you're making a good point. There has been a concerted effort within the FDA, working with both NCI and the American Academy of Pediatrics, to address the issue that was being brought up here. But the fact is that you won't have these products in Phase III trials for children. I mean, that just is not the process that happens for oncology drugs, though they're almost all--most of the children are in trials. It has to do with the paucity of, you know, the population and the ability to actually conduct Phase III trials.

I know this seems schizophrenic, so I just--so dealing with that issue, the quandary was we would never have products labeled for kids who have cancer which--yet we would have a tremendous amount of information. So there was an entire process and a number of meetings to look at how can we make the information available that is developed for this population. That's why there's a guidance on how to do that and how you can--and encourage the development of these products and research into

these products for children. And that's why the statement was that you don't actually have to have the product approved for children for certain indications to get this information into the label. But it is, you know, a product, a disease-specific process, and it's appropriate that information will go into the label for the oncology drugs.

DR. NELSON: But I guess if the comfort level in doing that is because there won't be the opportunity given the professional organization for extensive off-label use, then I guess as a group at some point in the future we should tackle about how one could discourage off-label use while at the same time providing information.

DR. McCUNE: That's one of the reasons why I wanted to point out in the boxed warning that it does state that a qualified physician using anti-neoplastic therapy be the one to administer the drug.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: Well, you know, this is a real quandary because you're absolutely right that

the vast majority of children are on these studies, which is wonderful because they are being monitored very carefully. The ones that don't make it on to the protocols are usually, in my opinion, ones with comorbidities or some--or there's such an advanced disease. So they're starting to treat them with these things.

I'm wondering if given the fact that a year doesn't--given the fact that there isn't a huge population of off-label use out there, a year's data doesn't give us very much of a chance to see off-label problems. Do you see what I mean? If they're treating--a million kids were treated with something in that year, then you've got a pretty good idea--a pretty good chance to pick up anything that was somehow missed in the clinical trial. But if it's a very small number of kids that were treated in that year, then we really don't have very much of a chance of picking up anything either.

DR. McCUNE: The division continues to follow reports associated with the use of this

drug, so it's not like we don't have any follow-up. But we just wouldn't come back to present it necessarily to you unless there was something that would be--

DR. O'FALLON: You don't diminish your surveillance. You just diminish your reporting to us. Is that what we're talking about?

DR. McCUNE: That's correct.

DR. MURPHY: Well, we diminish going back and reporting to you. We don't go back and look at the, you know, trials that you've already seen. I mean, since that process has occurred. If additional studies had come in, you know, there might be an opportunity. But I think the only thing I would say is that if there's something that concerns you in the report and it was combined with the issue of either a small population or, as some of you know from the prior committee, the exclusivity is granted before the approval sometimes. That's changing because of the timing on the approvals, but there may not actually be much postmarketing in some certain situations. If

those situations--if you are concerned about something and either of those two situations exists, you could recommend that we come back and report to you relevant to whatever, you wanted more time to see what was happening. I mean, that is an option I think this committee has actually utilized earlier on when we had a very short postmarketing period.

But, again, I think just having a short postmarketing period wouldn't be the only reason to do it. It would be because there was a question or some concern that you would like us to come back and report to you about.

DR. O'FALLON: Isn't the purpose of postmarketing to pick up something that probably--that could have slipped through the cracks on the studies? That's all. If we don't give ourselves a very good chance at doing that, we're not going to have a chance to pick it up as much. That's all.

DR. MURPHY: Yes, I mean, and for the things you mentioned, I mean, the studies often--of course, the cancer studies--but, still,

particularly in other studies, they're much more exclusionary, and when it gets out there, it's used in the broader population. And as has been pointed out before, AERS is good over time picking up the rare, serious events that occur. So if those are concerns that you have, then you could recommend that we continue to report to you.

DR. CHESNEY: Thank you very much. Could I suggest that maybe we take a ten-minute break before the next speaker? I did want to ask if there was anybody here for the open public hearing. Nobody has registered yet, but we just wanted to check.

[No response.]

DR. CHESNEY: No. So I think if we could come back in ten minutes at 10 after 11:00, and we'll continue on with all the subsequent presentations. Thank you.

[Recess.]

DR. CHESNEY: I think we're ready to get started. It looked like we should be able to finish pretty close to our allotted time for those

with appointments with planes, trains and automobiles at the end of the meeting. So we'll move on to the next presentation.

DR. McCUNE: Thank you. It gives me great pleasure to introduce Dr. Jane Filie. Dr. Filie is a general pediatrician and pediatric rheumatologist. After years of doing basic research on connective tissue disorders and genetics at the NIH, Dr. Filie was a pediatrician in private practice prior to joining the FDA.

Today Dr. Filie is going to talk to you about desloratadine.

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DR. FILIE: Thank you, Dr. McCune.

Good morning, everyone. I would like to present the adverse event review for desloratadine during the one year post exclusivity.

Desloratadine is an antihistamine by Schering Corporation. It was originally approved in December 2001, and pediatric exclusivity was granted in February 2003. It is indicated for the treatment of seasonal allergic rhinitis in patients 2 years and older, and for the treatment or

perennial allergic rhinitis and chronic idiopathic urticaria in patients six months and older. The recommended doses are listed on the slide.

I would point some facts regarding loratadine, which is the predecessor of desloratadine. Loratadine is approved for children 2 years and older, whereas desloratadine is approved for children 6 months and older. Desloratadine is the major metabolite of loratadine and possesses similar pharmacodynamic activity. It also has less extensive first-pass metabolism and a longer half life than loratadine.

Now, the drug use trends for desloratadine. It accounted for 15 percent of the prescription non-sedating antihistamine market from March 2003 to February 2004. The total number of prescriptions increased slightly from 9.8 million to 10.2 million during the same period. Pediatric prescriptions accounted for 1.3 million prescriptions.

For pediatric exclusivity 246 children, 6 months to 11 years of age were exposed to

desloratadine in three two-week, double-blind, placebo-controlled safety studies. The efficacy of the drug was extrapolated from the adult efficacy data. The safety studies identified a subset of pediatric patients who are slow metabolizers of desloratadine, approximately 6 percent of all pediatric and adult patients, and 17 percent of the African-American patients. There was no difference in the prevalence of poor metabolizers across age groups, and there was no significant difference in adverse events, laboratory tests or vital signs between the pediatric poor metabolizers and normal metabolizers who received desloratadine or placebo.

The adverse events that occurred more than 2 percent during the clinical trials, which included adults and children over 12 years of age are listed on this slide.

In the pediatric clinical trials there were no adverse events reported that occurred more than 2 percent of patients in the age group of 6 to 11 years of age. The adverse events that occurred more than 2 percent in frequency greater than

placebo are listed on the slide according to different age groups as well.

During the one-year post exclusivity, there were 185 reports for all ages. Among the 185 reports there were 20 pediatric reports, 6 of them in the United States. Among the 20 pediatric reports, there were five serious pediatric event reports and there were no deaths.

The pediatric adverse events reported are listed on this slide. Even though there were 20 reports, these events do not add to 20 because some reports contained more than one event. The underlying events are unlabeled events.

I now proceed with a synopsis of the serious adverse event reports. 12 year old on desloratadine and nasal beclomethasone for unspecified allergy had bronchospasm and shortness of breath, hospitalized for an unknown period of time.

An 11-year-old on 5 milligram desloratadine, unknown indication, developed two asthma attacks within one month requiring

hospitalization. The patient had five doses of the drug between the asthma attacks without difficulty.

And a 6-year-old on desloratadine, 2-1/2 milligrams daily for urticaria, presented with Kawasaki disease three months after the initiation of treatment.

A 5-year-old on 1.25 milligrams desloratadine daily for cough and nasal secretion experienced somnolence, bradycardia, diplopia, dizziness and motor uncoordination, and this patient was hospitalized for 12 hours.

Last: a 2-year-old with a history of bronchiolitis and wheezing on desloratadine, 1.25 milligrams, for coughing and rhinitis, who experienced status asthmatic as requiring hospitalization on two successive days.

Notice that these were all non-U.S. cases.

Although not reported as serious adverse events, there are a few adverse event reports that were clinically significant. For example, a 5-year-old on desloratadine, 125 milligrams daily for rhinitis, experienced two days later somnolence,

disorientation, and an unspecified extrapyramidal disorder, one week later became unconscious, and recovered one day after the drug was discontinued.

Another relevant case was a 4-year-old girl on 2-1/2 milligrams of desloratadine daily, had been on the drug for a week from mosquito bites and no other medications, experienced spasms of the upper body which resolved weeks later after discontinuation of the drug.

Lastly, a 3-year-old on desloratadine for 8 days of a known dose and specified medication, no concomitant medications, experienced torticollis, and no other data was available.

Also notice that these are all cases that occurred abroad.

In summary, there were a few pediatric adverse event reports during the pediatric exclusivity period. There are no new safety concerns regarding the use of desloratadine in the pediatric population. This completes the one-year post exclusivity adverse event monitoring, as mandated by BPCA, and the FDA will continue its

routine monitoring of adverse events for this drug.

DR. CHESNEY: Any questions? Yes, Dr. Newman.

DR. NEWMAN: I have two questions. You listed a whole of kind of common pediatric things that were listed as more commonly occurring with medication than placebo. Were any of those statistically significant?

DR. FILIE: Which--

DR. NEWMAN: This was in the exclusivity trial, the fever, diarrhea, upper respiratory tract infections, coughing, all of those things. It's your ninth slide. Greater than 2 percent in frequency, greater than placebo.

DR. FILIE: No. These were really not so much different, and the range, the incidence of these side effects, adverse events, was around not more than 4 percent each, and they were not really clinically significant.

DR. NEWMAN: But all of these were more frequent with drug than with placebo?

DR. FILIE: Exactly. Which slide are you

talking about?

DR. NEWMAN: It's Slide 9.

DR. FILIE: Yes. These did occur more than 2 percent, and more frequently than placebo.

DR. NEWMAN: And were there some sort of equal number of adverse effects that happened less often with medication than placebo? I mean, I don't know how--if you look at 100 different things, and your standard is just more rather than statistically significant more, you'll find a bunch.

DR. FILIE: You're asking if there were some adverse events that occurred more frequently in placebo than with the drug?

DR. NEWMAN: Right.

DR. FILIE: Probably so, but I do not have the numbers. I cannot tell you that, but this is what is expressed in the label. Usually what they will have on the label is what occurs more frequently on the drug.

DR. NEWMAN: Unless you can tell how often it occurred with both and whether any of them are

significant, this kind of labeling just doesn't really help at all. It's not informative.

DR. FILIE: Yeah. Would anyone like to add? I would like to invite the Review Division if they would like to chime in and give any additional information. But as far as I can tell without looking at the reviews, the clinical reviews right now, I don't have the numbers.

DR. MURPHY: I think what you're getting at is how we do adverse event reporting in our labels. Is that the issue?

DR. NEWMAN: I'm just saying, you know, if you look for 100 different things and your only standard for reporting it is that it occurred more often with--I mean they're not going to occur at exactly the same rate with drug and placebo. They're not going to occur at exactly the same rate, so the fact that it occurs a little more with drug than placebo doesn't really indicate anything, you know. The question is does it occur either any one outcome statistically significantly more, or a lot more, or if you add them all together and say,

okay, any adverse event, was any adverse event, if you pool all these together, are one or more adverse events more likely with drug than placebo?

As a clinician who sees a lot of kids who get antihistamines and sees all of these things on the list every day, I mean a lot, I suspect that this is not a real association, but then why put it on the label? It just doesn't help me at all.

DR. MURPHY: What is done is if there are statistically significant differences in the trials, clearly that is put into the label, okay? But what is also then done--and one could argue the usefulness of that--but because trials are very, you know, as we've discussed, limited in number, limited in duration, limited in the population, what is also provided is additional information about adverse events that occurred more frequently in the treatment group than in the placebo group. I mean you're right from a mathematical point of view, but it is felt that because we know we're only looking at a limited amount of data that it is appropriate to define that which we think is

clearly statistically significantly different and that which we think is just reported that was seen in the clinical trials.

And actually there's been discussion of should we even be including those things that are 1 percent--what percentage should we have a cutoff and how useful it is? But that is some of the thinking behind why doing it, is that you don't really know what the entire context--I mean the entire spectrum might be, and this is the controlled clinical trial against placebo, and you know that in a population you're going to have background noise, so at least you can report against placebo what was seen.

Is Badrul here? Would you like to comment on how your division reports, particularly I think for the antihistamines. But it gets to the bigger labeling issues.

DR. CHOWDHURY: I'm Dr. Badrul Chowdhury, the Division Director in Pulmonary and Allergy Drugs.

What you're asking is a pretty broad

question I think, is not necessarily applicable to this drug as a single entity that applies across how an adverse event is reported in the product label following clinical trials.

The general practice is--I mean knowing it's a very limited database for a clinical trial, it's usually a few hundred to thousands, and you cannot really capture everything that has happened or could happen. The practice generally is to look at the numbers that happened with the drug, look at the numbers that happened with placebo, and make some reasonable cutoff of event that is more commonly happening with drug than with placebo, and put the numbers then.

Statistical influential statistics on adverse events is completely useless because you cannot really put a p-value against an adverse event and conclude it is significant or not. It really isn't worth an observation. And it is really during clinical practice that more and more is known, and adverse events, as it is reported, gets modified. It is not uncommon for a drug to

have an adverse event that you did not think of as being a drug-associated adverse event, but later on there's cases it bears out to be the case.

DR. NEWMAN: I would disagree with that, that there's no way that in practice anyone would pick up any of these adverse events as being drug related in the absence of a randomized trial because the background noise for all of these things is a lot.

DR. CHOWDHURY: Nobody's saying that is drug-related or drug-causes adverse events. It is just that these were observed. And add that to the interpretation of ultimate use because if you see something which is happening more commonly with the drug and not happening with placebo, I mean, it's not possible to go after each and every adverse event and try to make a cause and association if it is caused by the drug or not. I mean, just cannot happen in development in the limited time period. We're just reporting what was seen.

DR. NEWMAN: Okay. My guess is this is not the time to try to--

DR. CHOWDHURY: Oh, it probably is not, and this is really I think a more broader issue of adverse event reporting in the product label that comes out of clinical trials across drugs and across drug classes done specifically for desloratadine.

DR. NEWMAN: So maybe we could discuss it more at another time, but just as a consumer of this information, I find it pretty useless.

DR. CHOWDHURY: I mean I would really not discount it to that of an extent because I mean there are also adverse events that are here which actually may even turn out to be meaningful. I mean if I just pick an example for here, appetite increase. Somebody can say it's completely useless. But if you really go back and look at all antihistamines, it is not uncommon for some older antihistamines actually to cause persons to gain weight. This was the case with older antihistamines. Nobody would really link that association, but it is known that some older antihistamine which is not marketed in the U.S. any

more, actually caused increased weight.

And when you see in this report this appetite increase, I mean you can discount it being useless, but who knows? It actually may in the future might turn out to be useful.

So it's just a pure reporting of the number that were seen, not necessarily making a conclusion if that is associated with the drug or not.

DR. MURPHY: Again, it gets back to what do you think you're trying to achieve? I think the thought here is that, again, this is the controlled trial against placebo. You're going to have problems once it's out with all the confounders of background noise, and that it's appropriate to let people know in a controlled trial, this occurred more frequently than placebo, not making attribution. But over time you may, as Badrul pointed out, we will come back and revisit that which has been labeled from controlled trials and see if it's becoming relevant or more relevant. I guess better more relevant.

DR. CHESNEY: Thank you. I think this could be something that was readdressed, and Dr. Ebert and Dr. Nelson have questions. I also.

I've wondered, what stands out to me here is the movement disorders. What do you make of that, and is that a common finding in other antihistamines. I'm not used to using it to prevent them.

DR. FILIE: Usually it is not common to occur with antihistamines, but these are newer generations of antihistamines. It was not described in the clinical trials either adults or children. This was never described. So this is why we brought it up as important, and again, we need to report the information as it is and the numbers as they are, but, yeah, it had not been described in the clinical trials for adults of children. The earlier generations, like super heptadine, which was an older antihistamine, was known to cause some purposeless movements in rats in preclinical studies. So again, this is something that I think we need to watch.

We're looking at an ocean and these little signals pop here and there, and probably only with time and more numbers, we'll be able to make a better interpretation of this.

DR. CHESNEY: Thank you. Dr. Ebert and then Dr. Nelson.

DR. EBERT: Could you provide a little more detail about the two cases of congenital abnormalities?

DR. FILIE: Certainly. Let me see if she can pull this. It's a back-up slide. Can you find it? It's called maternal exposures.

These were two cases, and again, these reports have very little information. They are very vague, and it's very difficult to make any attribution of congenital malformation and link this to the exposure to the drug. As you can see, one baby was born with cryptorchidism and hernia and was exposed to desloratadine for five days, unknown gestational age, and the mother had concomitant use of amitriptyline. And the other case was a baby born with a cleft lip and palate,

and was exposed to multiple medications for an unknown length of time and unknown period of the pregnancy.

So it's really very vague and difficult to make any assumption given even the background rate of the occurrence of these malformations.

DR. CHESNEY: Dr. Nelson and then Dr. Fant.

DR. NELSON: I think you correctly observed that these are isolated events in an ocean, but I'd like to comment on the size of the ocean. What strikes me is that these are non-USA reports that you're reporting, and that if we want to try to get some estimate of frequency that what we really need--and I guess I would be making Dr. Iyasu's job more difficult--the European Union, if that's where they're from, is a smaller market than United States, and in fact it may then reflect a higher frequency than we might think if we look at our 10 million prescriptions here. We don't know then how many prescriptions were actually written for the population that's reporting these events.

DR. FILIE: That is correct.

DR. NELSON: And it also raises an interesting question whether their ascertainment system's better or whether their physicians are just more socialized into--I don't use that term politically--into reporting, etc. But the data that is not comparable, we have isolated events out of a market that we don't have the denominator, and we have a denominator out of a market we have no isolated events. So either we're much safer here, or what? So comment.

DR. FILIE: Exactly, and I think you're correct.

DR. IYASU: Could I make a comment here? I wouldn't presume to sort of evaluate how different our systems are. I won't make a comment about that.

But in terms of foreign reports, what we get is probably a very small percentage of the actual volume because the requirements are there for serious events to be preferentially reported from those serious sources. There's no requirement

to. So there is also, you know, many--there's more focus on the serious events. But in terms of exposure, I don't know of any database that we have access to at FDA that will sort of estimate what the exposure that was in Europe, although they do have their own databases as well. And IMS has different streams that also is only probably making estimates in drug exposures in Europe.

So I don't think we have the right databases to try to tease out what the differences are, but I think we need to be careful, wherever the reports come from, that if there is an opportunity to explore them further, that would be an important activity which you say you would make my job more difficult. But I think this is something that we can entertain.

DR. CHESNEY: So you can add a European database to your American database in your spare time.

[Laughter.]

DR. CHESNEY: Dr. Fant?

DR. FANT: Just one comment that stems

from one of your case reports, and I think it just underscores the importance of these narratives, at least from what I can glean.

In the 5-year-old, who basically over the course--two days after starting the medication, over the course of a week, developed somnolence, disorientation, unspecified extrapyramidal disorder, which seemed to progress over a week to a state of unconsciousness, and then recovered one day after the drug was discontinued. What you told us was that one of the features of this drug was its relatively long half life. So it's just kind of perplexing, just from a pharmacokinetic standpoint how such severe symptoms--now they may be connected; this may be a connection, but it's kind of a strange one from the way I interpret this, and it's worth noting because it may be real or it may be something that emerges as some bizarre quality related to this particular drug in terms of the idiosyncratic reactions it may elicit in people. But I just don't understand how such severe symptoms can resolve in one day after being

on a drug with a long half life for a week.

DR. FILIE: Yes. I agree with you. And again, these reports are very vague, so it doesn't give us much information. And you're right, how could he just recover in one day how disoriented and somnolent this child was. Could be that this child would have been in that category if this all metabolized and really had a more significant presentation of the side effects. We just don't know and can't tell just from the report.

DR. CHESNEY: Thank you very much.

I think we'll move on to the next topic of adverse events for budesonide and fluticasone.

x

DR. CHOWDHURY: Moving on with the next section of the presentations. In this section you're going to hear information regarding adverse events that have been reported to the air system for budesonide and fluticasone containing products. These adverse events may have been reported by patients, physicians, health professionals or the companies themselves, and specifically they're reporting of these adverse events to you, the

Pediatric Advisory Committee, as I mentioned before, is monitored by the BPCA. It's only for one year, so you'll hear a lot of information from a series of presenters. So we'll have questions for clarification and also discussions of the question that has been posed to the Committee at the end of the series of presentations.

So you will hear from four speakers this morning. The first speaker is Dr. Peter Starke. Dr. Peter Starke is a pediatrician and a medical team leader in the Division of Pulmonary and Allergy Drug Products. He has been with the Agency since 2000. Dr. Starke will be summarizing the regulatory history and the labeling changes and will provide a perspective on the safety of these drug products which include the orally inhaled and intranasal budesonide and fluticasone propionate drug products. So this will give you I think a good background in context for the next set of presentations that will focus on the summaries of clinical trials as well as the adverse event reports.

Dr. Peter Starke.

x DR. STARKE: Good morning. I'm Dr. Peter Starke. As you've heard, I'm a pediatrician and a medical team leader in the Division of Pulmonary and Allergy Drug Products. This morning I will attempt to place the written request studies and the adverse event information, particularly the adverse event information that you're about to hear, into some perspective.

Although you will hear about adverse events with all the budesonide and fluticasone drug products, we're specifically going to deal with just the orally-inhaled and intranasal drug products, and not the cutaneous drug products, at least my talk.

I want to assure you that we've reviewed this information carefully and are comfortable with the adverse events that you'll hear discussed, that they're appropriately represented in the label for both of these drug products. In addition, many of these types of adverse events occur with other orally-inhaled and intranasal corticosteroids and

those two, as appropriate, appear in the labels for those drug products.

This is an outline of my talk. I'll set the stage for the discussion with some background on the burden or allergic rhinitis and asthma in the United States. I'll then focus on asthma and review what is considered appropriate and necessary treatment for persistent asthma as defined by the National Asthma Education and Prevention Program in cooperation with the National Heart, Lung and Blood Institute.

These guidelines for the diagnosis and management of asthma were first published in the early '90s and then again in 1997, and again in 2002. You see the URL for the website listed at the bottom of the slides.

Then I'll go into some of the regulatory history and labeling chronology. The labeling for these drug products has changed dramatically over the last 10 years and I'll show you a lot of what has happened in that time period. We'll go over the specific results of growth suppression studies

with both budesonide and fluticasone, covering the orally inhaled and then later the intranasal drug products, and then I'll touch on the status of the current labeling for safety findings for these products.

This slide shows you a little bit of the burden of allergic and non-allergic rhinitis in the United States today. Allergic rhinitis is a very common disease and it represents significant morbidity as you see shown. The figures you see come from the 1998 Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, and I'll touch later on their recommendations for us of corticosteroids in the treatment of allergic rhinitis. I'm not going to talk at all about non-allergic rhinitis.

However, we'll focus a little bit more on the burden of asthma. This information and the information on the next several slides comes from the National Information Survey which is conducted annually by the National Center for Health Statistics at the CDC, and this information can be

found on both the NHLBI and the CDC websites.

Asthma is a significant public health concern in the United States. It's associated with significant morbidity and mortality. In the United States it's estimated that over 20 million persons are affected including over 6 million children. You see on the slide the associated emergency department, hospitalization and deaths during 1999.

This slide represents the burden of asthma in terms of the prevalence per thousand population in the United States today. Again this comes from the National Health Interview Survey, and you can see that the questions on the survey changed after a period of time, and these questions represent slightly different questions after--I can't see the date from here, but something like 1999. Now, what you see is a rise in prevalence in asthma over time, starting in 1980 at about 31 per thousand, increasing by 1996 to 54 per thousand, an increase of about 74 percent.

Here you see the mortality rates for asthma in the United States over approximately the

same time period. This again comes from the same database. You can see that the ICD codes changed slightly around the year 1999 so they represent slightly different coding, but again give you a good sense of the mortality rates and what you see as an increase from 14.4 in 1980--this is per million--to a peak of 21.9 million, and then a decrease to about 16 million by the year 2000. So the peak prevalence was in 1995.

What I've shown you is that in the United States this represents, asthma represents a huge burden to individuals as well as to the health care system, and while the prevalence of asthma has increased and increased quite a bit since 1980, the overall increase in mortality has not reflected the same rate of rise as the increase in prevalence. The mortality peaked in 1995 and is now declining, and most practitioners feel that this is due to a combination of advances and care that are monitoring, patient education and the use of controller medications including the use of corticosteroids for persistent disease.

This slide represents a brief summary of the medications used in clinical practice for the treatment of asthma, and you see quick relief and long-term controller medications listed. I've highlighted corticosteroids and want to place their role into some--as a controller therapy into some perspective here. Originally the NAEPP guidelines recommended the use of controller medications for moderate and severe persistent asthma, but the latest recommendations now state that corticosteroids should be used for all forms of persistent disease.

Now I'm going to switch topics a little bit and start to give you a sense of what's changed in the labels over the last 10 years. All of these drugs were approved during the 1980s and 1990s including budesonide and fluticasone. There are a number of years during which some significant events occurred. The first was 1994. In that year the Pediatric Labeling Rule took effect, and that labeling rule did a number of things, but among the things that it did was that it required sponsors of

approved products to examine the existing data in the product label to determine whether the pediatric use subsection should be updated, and this prompted a number of pediatric efficacy supplements and many of these products were approved to lower age ranges down to about 4 to 6, and subsequently some lower.

In that same year the FDA began to review the labels for all orally-inhaled and intranasal corticosteroids and made a number of changes over time. They started doing it then, but over time have made a number of changes with the additions to the labels of adverse events as reported to the companies and to MedWatch.

Now, in 1997 several important events occurred. First the NAEPP expert panel issued their second report and I've discussed the results of their recommendations already, and you see them up here. Second major event was that a growth suppression study was submitted to the Agency, and this study was a one-year study with intranasal budesonide. The dose that was used was the highest

approved dose of 336 micrograms a day, and it showed a statistically significant growth suppression effect, but no significant effect on hypothalamic-pituitary-adrenal or HPA access function.

In addition, other growth studies were submitted and are published, but particularly they were submitted, and for both orally-inhaled and intranasal drug products, but particularly for the orally inhaled, and with this information several things occurred.

I'm going to skip over what happened and just talk briefly first of 1998, come back to the allergic rhinitis, and the Joint Task Force for Practice Parameters, in conjunction with the American Academy of Allergy, Asthma and Immunology recognized intranasal corticosteroids as the most effective medication for the treatment of severe allergic rhinitis.

Going back to asthma, because of the growth studies that came in a Joint Advisory Committee meeting was held. This was a Joint

Pulmonary Allergy and Metabolic and Endocrine Disease Advisory Committee meeting, at which time the results of the growth studies that had come into the Agency were discussed. They did recommend a number of labeling changes, and I'll show them to you in the next several slides. That included putting results of growth studies in the label, and adding class labeling for risks for adverse events to all labels for orally inhaled and intranasal corticosteroid drug products.

In November of that year, in November of 1998, the FDA implemented these recommendations, sent letters to each of the sponsors requesting supplements with additional labeling. Now, this is the labeling in two of three locations that was added to the labels, and as I just started to say, there are three locations on the label where labeling was added. You see the first two, the Precautions, general and the Adverse Reactions sections, and under Precautions, pediatric use section, a long paragraph was added.

I haven't shown you the whole paragraph.

I have it if you want to see it, but this is a synopsis of what was said, which is that: Orally inhaled or intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. The growth effect may occur in the absence of laboratory evidence of HPA axis suppression. The potential for "catch up" growth following discontinuation of treatment was not addressed. Growth should be monitored routinely in patients. To minimize the systemic effects, each patient should be titrated to his or her lowest effective dose.

Now, through our evaluations of growth studies, we've come to understand a number of important points about these studies. First, we feel that growth suppression reflects systemic exposure to the corticosteroid. This is likely to be due to a direct bone effect on osteoclastic-osteoblastic activity. That's a presumption that I'm saying. We believe it's a very sensitive indicator of systemic effects, and therefore, the potential to cause systemic toxicity. And that

effect may be generalized to adults as well as children. In other words, the growth suppressive effect, being an indicator of the potential for toxicity is not specific to just the growth population that's looked at in the studies.

I'm showing you where a growth defect study may be positive where an HPA axis study was negative. Because of the way we want the information, we request that these studies look at, as accurately as possible, and characterize the difference in growth rate in patients treated with active and with control. Now, they're quite technically difficult to perform, and I do want to congratulate both drug companies for having growth studies with the intranasal and the orally inhaled drug products, and I'm going to show the results shortly.

I'm not going to go into the details of the technical difficulties with doing them and/or assessing them, but keep in mind that these require at least a year on treatment, height measurements with stadiometry, and they must be performed during

the relatively level or flat growth phase, generally between 3 and 9 or 10 years of age, after the infant growth spurt and before the pubertal growth spurt.

There are a number of limitations to interpretation of these studies. They are not designed to demonstrate reversibility with continued use after a year or after stopping a medication. They're not designed to evaluate the effects on final adult height, and you cannot take the growth effect and relate it at all to the individual patient. For these reasons, they are very difficult to interpret out of context of the study itself.

All the studies were designed prior to when we published a growth guidance in 2001, and no two studies had the same design. Therefore, it's quite difficult to do any kind of cross-study comparison, and I won't attempt to do so.

So here's the growth study for inhaled budesonide. This is the design of the growth study. It used Pulmicort Respules. This is, by

the way, not in the label. What's in the label is the growth results for the 12-week study that gave the indication. This information, however, was discussed at the 1998 Advisory Committee meeting, and therefore I'm showing it to you now.

This was a 12-month open label extension of a 12-week double-blind study. The arms you see with inhaled budesonide and nonsteroidal. There were several analyses done for different age groups, 9 months through 3 years and 4 through 8 years. Before I show you the results, I just want to caution you about interpreting results for the 9 month to 3 year age range, where growth is not linear and where one generally has to measure length rather than statutory height, and this introduces a large variable into these kinds of studies.

So here are the results for the orally inhaled budesonide. You see at the top the 4- to 8-year-olds, and below it the 9 through 3-year-olds. You see also the budesonide and then the nonsteroidal groups below it, and the height

changes over the year--I'm sorry, the growth rate over a year. The delta is what I would point out to you. That's the difference between the active and control groups. A negative number implies a growth rate effect, a positive growth rate effect. So you see for the age range of 4 to 8 a growth suppressive effect of half centimeter, and for the lower age range, 1.8 centimeters. So there clearly is some difference between the two, but again, it's hard to interpret what that difference actually is.

This is the growth study using inhaled fluticasone propionate, and I believe this is in the labeling. This used the Flovent Rotadisk. It was randomized, placebo-controlled one-year study in prepubertal children. You see that two doses of fluticasone propionate were used in this study, 50 and 100 micrograms twice daily.

There are the results. There was some indication of a dose response in this study, and if you look at the first two lines of the delta you see the results compared to placebo for the 50 and 100 micrograms twice daily.

So just to continue and update from 1998 to 2004, the Advisory Committee recommendations were implemented, as I've shown you. I mentioned already that we published a draft growth guidance in 2001. Guidances represent the best thinking of the Agency, but they do not require sponsors to follow that thinking if they can show us some alternative methodology.

The labels have been reviewed and updated with new labeling supplements as they come in, with post-marketing adverse events as reported. You'll hear the pediatric exclusivity studies next. They're updated with pediatric exclusivity studies results as appropriate and with the results of Phase IV growth studies as they come in.

Here are the results for the intranasal budesonide and fluticasone growth studies, and you see the moiety on the left, the dose, the N, the growth rate over a year, the difference between active and placebo and the 95 percent confidence intervals when we have them. For convenience I put on the slide the results of the beclomethasone

study that started this all off in 1997, and you see only a very small effect for each of these two drug products. But I just want to point out the budesonide used the lowest approved dose; fluticasone used the highest. We do recommend at this point that sponsors use the highest approved dose in these studies.

So the labeling status as of 2004. All labels clearly describe the potential risks for adverse events; HPA axis studies. We've included the class labeling. There are some minor differences between various drug products in the wording, but that's probably fine. Growth studies, as they come in; and all the labels are being reviewed and updated as new labeling supplements are submitted.

Specific labeling for budesonide and fluticasone is shown in this slide. Both the orally inhaled and intranasal drug products for both of these drugs have HPA axis growth and post-marketing adverse events labeled. In addition--and this relatively new information, so I've included

it separately--budesonide--and you saw the results of the growth study. That study is now in the label as of the last month or two. In addition, as of the end of August, budesonide was relabeled as Pregnancy Category B, and this is as the results of information from three Swedish birth registries. You see a representative of what Category B, one of the requirements for Category B. It was changed from Category C to Category B.

So in summary, asthma is a chronic inflammatory disease of the airways. It represents a huge burden to the health care system. While the prevalence of asthma has increased since 1980, the mortality rates increased, and then have declined, although the overall mortality rate is higher now than it was in 1980. Corticosteroids are recommended as a primary controller therapy for persistent asthma, all forms, and as the most effective therapy for severe allergic rhinitis.

The types of adverse events that may be expected with this class of compounds, namely corticosteroids, have been well documented over the

years, and the FDA is continually reviewing and updating the labeling as we get more and more information about the individual drug products.

I've shown you how the labels have changed dramatically over the last 10 years with class labeling. We really haven't gone into HPA axis information, but you'll hear more about that in the written request studies. I've shown you about the growth studies. You'll hear about the adverse event data. At this point we believe that the current labeling for these drugs is concurrent with the latest safety data for these products.

I leave you with this quote from the NAEPP guidelines, from the 2000 guidelines, which state that: "Inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma," and obviously with severe, "and the potential but small risk of delayed growth is well balanced by their effectiveness."

Thank you.

Now I'm going to introduce to you Dr. ShaAvhree Buckman. She is a pediatrician with the

Division of Pediatrics. She has Ph.D. training in molecular cell biology and pharmacology. She's been a medical officer in the Division of Pediatrics for the last two years. She will be presenting on the clinical studies for budesonide and fluticasone.

x DR. BUCKMAN: I can now say good afternoon.

[Laughter.]

DR. BUCKMAN: I will be presenting a summary of clinical trial data for fluticasone and budesonide. As an overview this table describes the various fluticasone dosage forms, the original dates of approval and current pediatric approval information. This table includes topical, intranasal and orally inhaled products.

The most recent approval, as of May of 2004, was for Flovent HFA Meter Dose Inhaler. HFA stands for hydrofluoroalkane, and this inhaler is designed with a CFC-free propellant that is more environmentally friendly.

This table describes the various

budesonide dosage forms which include orally inhaled, intranasal and oral products. Because the names of some of these products can become confusing, the slide just shows some examples of some of these products. The Advair Diskus, Flovent Rotadisk and Pulmicort Turbuhaler are inhaled powders. Pulmicort Respules are a solution for inhalation used in conjunction with compressed air-driven jet nebulizers. Also shown here is a typical Flovent Metered Dose Inhaler which delivers aerosolized drug, and Entocort, which is shown in the corner, is indicated for oral use only in adult patients who have Crohn's disease. We will not be discussing this product during today's presentation, but it is a budesonide containing product. Also shown here are two nasal preparations, Flonase as well as Rhinocort Aqua.

Seven dermatology and pulmonary studies were requested for pediatric exclusivity for the fluticasone moiety. Four studies were requested for Cutivate, which is the dermatologic product. One study was requested for Flonase, two studies

for Flovent, and there was also requested an in vitro study report as well as a population PK report for Flovent.

First we will discuss the studies for Cutivate. As background, Cutivate cream has been approved for use in children 3 months of age and older since June 17th of 1999. A written request was issued for other fluticasone containing formulations on June 25th of 1999. This written request included three studies for Cutivate lotion and one study for Cutivate ointment. Also as background, an Advisory Committee was held in October of 2003, which many of you may have attended, that discussed the clinical risk management of HPA axis suppression in children with atopic dermatitis who are treated with topical corticosteroids. Presently, only Cutivate cream is indicated for pediatric use, not the ointment.

The current labeling for Cutivate cream includes studies which were not requested for pediatric exclusivity. 43 pediatric patients were treated with Cutivate .05 percent cream for atopic

dermatitis covering at least 35 percent of their body surface area for four weeks. 2 out of the 43 patients had HPA axis suppression, and follow-up testing was available for one of those two patients, which demonstrated a normally responsive HPA axis on follow up.

This study using Cutivate ointment was requested for exclusivity. 35 pediatric patients were treated with Cutivate ointment for atopic dermatitis covering at least 35 percent of their body surface area for three to four weeks. Subnormal adrenal function was observed with cosyntropin stimulation testing in 4 of the 35 patients. The recovery of adrenal function in these patients was unknown and follow-up testing was not performed. This information was incorporated into the Pediatric Use subsection of the labeling as shown here. It is important to note that Cutivate ointment is not indicated for pediatric use.

Now we will discuss the clinical studies for Flonase, the intranasal product. This study

was described to you briefly by Dr. Starke in the previous presentation, and it was not requested for pediatric exclusivity. This was a one-year multi-center placebo-controlled trial looking at longitudinal growth of 150 children, ages 3 to 9 years with perennial allergic rhinitis.

The mean reduction in growth velocity after one year of treatment with Flonase at 200 micrograms per day was estimated at .137 centimeters per year. HPA axis evaluation in these patients showed no interpretable effects on urinary free cortisol. And this study supported safety in children at the maximum approved dose and twice the daily dose typically used in patients at this age group.

The recommendation was made for the results of this one-year growth study to be incorporated into labeling, and you can see where this was incorporated.

This study for Flonase was requested for pediatric exclusivity. It was a six-week, multicenter, placebo controlled HPA axis study in

65 patients between the ages of 2 and 4 years with allergic rhinitis. 12-hour urinary free cortisol was used to evaluate the HPA axis. The results of this study were deemed indeterminate due to limitations in urine collection and wide variations in baseline urinary free cortisol levels between treatments groups. Therefore, no labeling change resulted.

Now we will discuss clinical studies for Flovent. We have discussed studies for Cutivate and Flonase, and now we'll briefly touch on an in vitro study report that was done for Flovent for exclusivity.

Prior to starting the clinical program with Flovent, the sponsor performed a comparison of the particle size distribution by cascade impaction for Flovent CFC Metered Dose Inhaler with and without the use of various spacers as shown here.

The results appear to indicate that the in vitro respirable particle content was similar whether the metered dose inhaler was studied alone or in combination with either of three different

spacers. However, the study was unable to evaluate factors that would have been important to the in vivo clinical setting, and this would include variations such as variations in flow rates, delay between actuation of a dose and actual inflow, how long a mask was held over the nose and mouth of a child, and therefore, result of this study were not incorporated into labeling.

These studies for Flovent were requested for pediatric exclusivity as well. Two 12-week placebo controlled efficacy and safety studies were performed in children with symptomatic asthma, who were between 6 and 47 months of age. Detectible plasma levels of fluticasone were seen in 13 of the placebo treated patients. Therefore, it was impossible to evaluate the actual extent of patient exposure and made the interpretation of the PK/PD relationship difficult to assess. The interpretation of this study was that it was impossible to determine whether the studies derived an accurate estimate of either safety or efficacy, and therefore, no labeling change resulted from

these studies.

Now we will discuss the clinical studies for budesonide. Two studies were requested for exclusivity. One was a safety study of budesonide nebulizing solution for the treatment of asthma in children 6 months to 1 year of age, and the second was an HPA axis safety study of the budesonide nasal spray in children between 2 and 6 years of age.

First we will discuss the studies for Rhinocort Aqua, the nasal spray. This was a 6-week multicenter placebo controlled study to evaluate the effect of Rhinocort Aqua on HPA axis in patients with allergic rhinitis. 78 children were studied between the ages of 2 and less than 6 years of age. The HPA axis function was evaluated by low-dose cosyntropin stimulated plasma cortisol measurements at baseline and following six weeks of treatment. The results of this study were deemed indeterminate because of difficulties in determining patient compliance, and no labeling change resulted.

Now we will discuss a clinical study for exclusivity using Pulmicort Respules. This was a 12-week randomized placebo-controlled study to evaluate the safety of Pulmicort Respules at .5 and 1 milligram daily in pediatric patients with mild to moderate asthma or recurrent persistent wheezing. 141 patients were studied between the ages of 6 and 12 months. The main safety concerns that were evaluated were concern for HPA axis suppression and suppression of linear growth.

Of the 141 patients that were randomized, 76 patients had an ACTH stimulation test at the beginning and the end of the study. The mean values of the three treatment groups did not indicate any difference in adrenal responsiveness. However, six patients with Pulmicort Respules and one patient in the placebo group had post-ACTH plasma cortisol levels that were below normal.

There was also noted in the bottom study a dose-dependant decrease in growth velocity between the placebo and budesonide treated groups. Also of note, pneumonia was observed more frequently in

patients treated with Pulmicort Respules than placebo. Three patients were noted in the budesonide treated group who developed pneumonia during this study.

These findings were incorporated into the clinical pharmacology and precautions subsections of the label show here. In summary, the studies for pediatric exclusivity have resulted in labeling changes for fluticasone and budesonide containing products. Pediatric trials for fluticasone and budesonide have identified important safety concerns which have been incorporated into labeling.

This concludes my presentation, and I thank you for your attention.

The next presentation will be given by Dr. Joyce Weaver, who is a Safety Evaluator in the Division of Drug Risk Evaluation in the Office of Drug Safety at the FDA. She will be presenting the adverse events for budesonide and fluticasone.

x DR. WEAVER: Good afternoon. I'm going to be presenting both use data and information about

adverse events reported to the FDA's Adverse Event Reporting System for budesonide and fluticasone.

First I'll talk about budesonide. The total number of prescriptions dispensed for all budesonide products increase from approximately 6 million in 2001 to 7.8 million in 2003 with pediatric patients accounting for about 29 percent of the total prescriptions. Rhinocort, the nasal product, is the most commonly used budesonide product, accounting for over half of the budesonide prescriptions, and of those, 17 percent were for pediatric patients.

The inhalation product, Pulmicort Respules, represents most of the rest of the prescriptions for budesonide. Over half of the Pulmicort prescriptions are for pediatric patients. Entocort represents a very small portion of budesonide dispensed.

The FDA's Adverse Event Reporting System, or AERS, contains about 2,800 adverse event reports for all ages covering the lifetime of the budesonide products. For the one-year period

following approval of pediatric exclusivity, AERS contains 157 cases including 38 pediatric cases. The pediatric cases did result in some serious outcomes including one death.

For the pediatric cases reported to us in the year after approval of exclusivity, we received more reports for boys than for girls, and most reports were received for children 2 to 5 years of age, and most reports were received for the inhalation product.

This slide shows the most commonly reported events in the pediatric cases in the year after the granting of exclusivity. Convulsions were reported most. Additionally, a number of events were reported that are indicative of systemic absorption of budesonide. Seizures are not an expected reaction with the use of budesonide. And when we looked at the cases we did not see a clear relationship between budesonide use and the subsequent development of seizures. One case was confounded by concomitant use of theophylline, and that case did not include a

theophylline level.

Two cases were not confirmed by health care professionals and the seizures were not well described. One patient was receiving CNS radiotherapy, and that same patient was receiving another drug concomitantly that is labeled for inducing seizures.

We have 17 cases showing possible systemic steroid effects including growth retardation, decreased blood cortisol, adrenal suppression and Cushing's syndrome.

As I said, we did receive a report of a death in the year following approval of exclusivity, and this case was reported from within the United States. It was a 3-year-old girl who had received Pulmicort Respules for 3 months. She stopped breathing, was transported to an emergency room, and she died in the emergency room. An autopsy was performed but not establish a cause of death.

We conclude from our review of the events reported to AERS for budesonide in the year

following approval of pediatric exclusivity that first, most events, including systemic steroid effects, are included in product labeling; and second, the convulsions are not labeled, but we didn't see a clear relationship to budesonide.

Now I'll go on to fluticasone. First, this is use data for fluticasone cream and ointment. Children account for about one third of the prescriptions for these products.

This is for fluticasone nasal spray. Prescriptions for nasal spray have remained fairly consistent over the past two years, with about 15 million prescriptions in 2003, and pediatric patients account for less than 10 percent of all prescriptions for fluticasone nasal spray.

This slide shows information for inhaled fluticasone. For inhaled fluticasone there are about 7 million prescriptions in 2003, and there;s been a downward trend over the past couple years. pediatric patients account for about one quarter of the prescriptions for the fluticasone oral inhalation products.

Now, to Advair. We're looking at this one separately. Advair's a combination of fluticasone and a long-acting beta-2 agonist, salmeterol. use of Advair has increased considerably over the past few years. Advair accounted for 17 percent of orally-inhaled steroid prescriptions in 2001. This increased to 54 percent in 2003, with pediatric patients accounting for 13 percent of total prescriptions.

Looking at the adverse events reported for all fluticasone containing products, AERS contains about 4,600 adverse event reports for all ages covering the lifetime of the fluticasone products. For the one-year period following approval of pediatric exclusivity, AERS contains about 2,100 cases, including 128 pediatric cases. The pediatric cases did result in some serious outcomes, including 5 deaths.

For the pediatric cases in AERS in the year after approval of pediatric exclusivity, we received most reports for children 6 to 11 years of age, and most reports were received for the

combination fluticasone and salmeterol product, Advair. You can see in the right-hand column, 82 of the cases that we received, 82 of the 128, were for reported events for that combination product.

This slide shows the most commonly reported events in the pediatric cases in the year after the granting of pediatric exclusivity. We looked at these cases and we found two issues. emerging from this.

The first issue we found was systemic steroid effects. There were 12 cases showing systemic steroid effects, and I'll address this issue in a couple minutes. The second issue in the cases was worsening asthma symptoms with the use of Advair. We had 22 such cases reported in the year following the granting of exclusivity, including four cases in which the patient died.

So first we will address the cases reporting worsening asthma symptoms with the use of Advair. And as I said, we received 22 of these cases in that one-year period. In 10 cases serious outcomes were reported, including four deaths. The

patients were 5 to 14 years of age. Race was not reported in most cases. The time to onset of symptoms ranged widely from the very first day the Advair was used to after two years of use. And the AERS cases do not show what the relative contributions of underlying disease and the use of Advair may be in the adverse event.

I'll present the four cases on which the patients died. The first case is a case originating from the United States. A 14-year-old black male was prescribed Advair after an episode of respiratory arrest. He had received Advair Diskus for 2 years when he experienced an acute asthma attack. He was transported to an emergency room. When he arrived he was in full cardiac arrest and he died. No autopsy was performed.

The second case also originated from the United States. This is a 13-year-old white male who had received Advair for about 6 months. He experienced an asthma attack and he died. An autopsy showed chronic bronchitis, hypertrophy of bronchial muscle, infiltrate of eosinophils, mucus

plugging of smaller airways, areas of pneumonia and air trapping.

The next case originated from outside the United States. A 14-year-old asthmatic girl was treated with salmeterol for an acute asthma attack. When she did not respond quickly to the treatment with salmeterol, treatment with a combined salmeterol fluticasone product was started. About 2 hours after her first dose of the combination product, the patient's condition worsened and she died.

The final case is a case, once again from the United States. A 13-year-old boy experienced cardiac arrest and died after receiving Advair for an unknown period of time. The report stated that while talking to a friend on the phone, the boy just stopped talking. An autopsy showed only lung changes consistent with asthma.

You saw this slide before. I'm showing you this slide again to remind you that most of the cases we received in the year after the granting of exclusivity were received for the combination of

fluticasone and salmeterol product, Advair. And once again, it was 82 of 128 cases. And while the use of Advair has been increasing in children, we don't think that the increased use explains the increased reporting in pediatric patients for the product.

This slide shows the pattern of reporting of pediatric adverse events with Advair, and the timing of important regulatory action and an important labeling change for Advair. Going across the bottom of the slide, each column is a quarter. So we start with a quarter in 2000 and go up to the first quarter of 2004. In January 2003 the FDA released a talk paper discussing the cessation of a salmeterol safety study, and the interim analysis of that study suggested that salmeterol may result in worse asthma outcomes. And in August 2003, Advair received a boxed warning about the possibility of worse asthma outcomes with salmeterol. And as you can see, the spike in reporting for Advair occurred around the time that Advair received that boxed warning.

This slide just shows the boxed warning in the Advair labeling, and again, the boxed warning was incorporated into the labeling because of the interim results of the safety study, not because of the AERS cases. So that's the first issue with the fluticasone containing products.

Now I'll address the other issue that we found in the pediatric cases, and that second issue is the systemic steroid effects with the use of fluticasone containing products. We had 12 such cases, including a case in which the patient died.

Now, to look at these cases a little more closely, most of the cases occurred with inhaled products. In one-half of the cases the patient was receiving more than one source of steroids concomitantly, and we had only one case that reported a systemic effect with the use of a product within labeled dose and without an additional source of steroids on board.

As I said before, we did have a case with an outcome of death. This case originated from outside the United States and we don't have

clinical details about the case. An 8-year-old girl, who used an unknown amount of a fluticasone containing product for an unknown dose, unknown period of time, developed adrenal crisis and died.

So what can we conclude from the cases that we've received for fluticasone containing products in the year after the granting of exclusivity? Most of the events reported are included in the labeling, including systemic steroid effects and including worsening asthma with the use of salmeterol containing products. In the AERS cases of asthma exacerbation with Advair, the relative contribution of underlying disease and Advair to the events is not known.

That concludes my presentation.

You've already met Dr. Chowdhury, but I'll introduce him again. Dr. Badrul Chowdhury is the Director of the Division of Pulmonary and Allergy Drug Products. He's been with the Agency since 1997. He's an internist, an allergist and an immunologist, and he'll be summarizing the pediatric programs for fluticasone and budesonide

that were presented previously.

x DR. CHOWDHURY: Thank you for the introduction, and I will very briefly summarize the programs that were done for fluticasone and budesonide containing drug products for allergic rhinitis and asthma indications, which are the nasal products and oral inhaled products. I'll go through them so that you can really put the presentations that you heard before, three of them, into context of the whole drug development programs and where we stand currently with the labeling status of these drugs, particularly for children.

Asthma and allergic rhinitis, as you have heard before, are common diseases, and in fact they're pretty common in children and impose significant burden on the health care system and also on individuals who have these diseases. And the prevalence of atopic diseases in general and asthma has been studied in depth. The prevalence of this disease is increasing, but recently, as yo have heard before, the trends in death and hospitalization are declining. And the various

factors which are contributing to this good outcome of a serious disease, including availability and use of various controller medications.

As you've heard before, corticosteroids currently are the primary controller therapy for all grades of persistent asthma, and they're being used, and their use is also being covered under various guidelines. For allergic rhinitis, again, corticosteroid is considered to be the most effective therapy.

These drugs, of course as we know now, are not completely free of adverse events. The topical drugs are applied on the surface or the body, and historically at one time they were considered to be really surface acting and not systemically active, but now we know that they are systemically active, and has adverse events, which came back to the systemic exposures, particularly those allergic to suppression of the HPA axis and also other metabolic effects. But the benefits of these are appropriately labeled and overall the risk/benefit supports the use of these drugs.

Now, I think we may have skipped a slide. Yes. I will, on the slide, very briefly go through the pediatric development of these drugs so that you can put the studies that you have heard in the context. Usually for asthma and allergic rhinitis these drugs are developed for adults first, and then the efficacy and safety goes down to the pediatric patients usually be generating data and by extrapolation, because we think the diseases are same in adults and children and the effect of the drug on the diseases are also the same.

Now, in going down in the age, one important consideration is to identify appropriate dose. Because this is surface active, therefore PK is not a good marker for dose selection. They are usually done through clinical studies, and for these diseases, asthma and allergic rhinitis, it is often quite difficult to design appropriate studies with efficacy endpoint, but again, they are being done to pick the right dose, and the aim here being, both for adults and also for children, to have a reasonably low effective and safe dose, and

then particularly for the children, show established safety of that dose.

So safety is a key in going down in the ages for these drugs, and safety assessment is done in a variety of ways and you have heard some of them. To summarize them here in the slide, we look at clinical trials and monitor them for adverse event, laboratory parameters, ECG findings, et cetera, and then look at HPA axis in varieties of ways, such as ACTH simulation test or look at plasma cortisol and urinary cortisols.

And these, which means the clinical studies and safety assessment of HPA axis are done pre-approval. Then the growth study comes in, process of linear growth, which really is a surrogate of systemic effect, and they're usually long studies, quite difficult to perform and interpret, and they're usually done post-marketing as a Phase IV. And then of course, after marketing, we look at post-marketing adverse events.

So the next three slides I'll quickly go

through these three aspects which is HPA axis safety, linear growth and post-marketing adverse events, and put some comments of mine on these three areas.

You've heard the pediatric studies which was done for specificity presented, and typically for asthma for both of these drugs, they were efficacy studies. And the ages that we ask for for efficacy study at the time we solicited request was based on what we already knew and what we wanted to know. For example, for budesonide, it was one year and below because the drug was already at that time approved a study for one year and above. For fluticasone it was 4 years and below for the same reason again, the drug was studied and indicated for 4 years and above.

For allergic rhinitis the study was a 6-week study primarily designed to look for safety, which means all kind of safety, adverse events reporting, clinical monitoring for adverse events, and also HPA axis safety. I will not go through the results of these. You've already heard Dr.

Buckman present results. Some of them are reflected in the label and some of them are not, and we made the decisions on a case-by-case basis, looking at the study, what we could come out from the study in terms of what could go on the label, and appropriate labels have been updated.

For assessment of systemic effects, as I said before, it is done really by two ways. One is assessment of HPA axis directly by either a stimulation test or by measuring cortisols in the plasma or urine, and these are done pre-approval, and for these drugs, generally they're negative, but again, not all. If you look across the drug classes, the product labels are quite different and they reflect the studies in the product labels.

And the growth study which, as you've heard before, you're studying the systemic effect and systemic toxicity perhaps, was also done for these drugs, and their effects are quite numerically small, and they're again reflected in the product label.

On the post-marketing side for adverse

events for these drugs, the large number of adverse events which is not unexpected, is systemic corticosteroid effects or effects related to suppression of HPA axis. These are expected and these are labeled, and these were seen in the HPA axis studies and also in the post-marketing studies, and the current label reflects these potential systemic adverse events.

The worst thing for asthma with Advair is something which is noted in the product label quite prominently, and whether it is coming from salmeterol contributing or whether it is coming from the fact that Advair is typically used for patients who have more severe asthma is currently unknown. One can speculate it can be either/or. Perhaps the patients with asthma who are more severe are put on Advair; therefore, having worsening of asthma is not necessarily very unexpected. And we also know recently that continued use of beta agonist, specifically salmeterol, can worsen asthma. Again, these are known adverse events that we know of now and is

adequately reflected in the product label.

To summarize this whole pediatric studies that we have, the safety concerns would be use of oral inhaled and intranasal corticosteroids, specifically budesonide and fluticasone which we are discussing today, are well characterized, so we know what the adverse events of these drugs are, and they're adequately described in the product label. The new data that we have obtained under pediatric initiatives in post-marketing adverse events are reassuring because we are not really seeing anything new which is totally unexpected. What we are seeing is what we expected to see, and they're not extremely, extremely common, and these are again adequately reflected on the product label.

So this risk/benefit assessment, these drugs of course have some adverse events, have some risk, and we think it is adequately reflected on the product label, and overall benefit of the drug is justified and well balanced with a safety and risk assessment of these drugs.

Thank you very much, and with this, I'll stop.

DR. CHESNEY: Thank you very much to all the speakers. A very, very comprehensive review of these two products. Questions from the panel? Yes, Deborah first, and then Dr. Fant.

MS. DOKKEN: I want to ask this question just because I have to leave in a few minutes, but as a lay person I have been scrambling to keep up during this discussion. And one of the things that struck me despite the overall conclusion that the results were reassuring, was of course both the rise in the use of Advair and the worsening of asthma, those adverse events reports. But then the fact that the labeling was changed, and somewhat for clarification for myself as a newcomer to this Committee, but also as I guess a consumer concern, when the labeling was changed due to the adverse events, would that be a trigger for the MedGuides that we talked about yesterday? I guess I think in particular because of the prevalence of asthma and the growing numbers, but also I think those of us

who either have children who have asthma or know families, there are a number of families who are very active if their children have asthma, and are good advocates. So they would be cognizant and would take note of information if it was made available to them in a way. So that's my question about the MedGuides. Would those go hand in hand or subsequently with a change in labeling?

DR. MURPHY: A Medguide is not tied any particular change. It is something that is, the decision that is arrived at depending on the circumstance, so it is an independent decision.

Badrul, do you want to talk about any products that have MedGuides?

DR. CHOWDHURY: I don't want to comment to the MedGuide here. The issue is that you are right, that when a box warning or some significant labeling or a doctor letter goes out, which had happened for salmeterol-containing products. It is quite likely that will increase the adverse event reporting by physicians or by patients.

And about the use of Advair and use of

Advair in children, I mean it is somewhat high, and whether it is a good or a bad thing is very difficult to actually conclude and say. You've seen for pediatric requests we did not particularly request studies for Advair. We requested study for fluticasone and not for the combination product, because we do not think that use of Advair in very young children is something which should be really routine because there are very difficult to titrate the combination products, you actually have one product. And we thought in children it's not really very appropriate drug to use. But we also know that Advair is very, very commonly used, and is actually quite commonly used in children and there are three dose strengths available. And often physicians and patients may not go down on the dose when their asthma is controlled.

So I think we have put down enough information in the label, and also there have been some dear doctor letters and some of the public forums where we have spoken about it, and we discourage the use of particularly high dose Advair

if it's not necessary, and also not to use the combination products in very young children where you want to titrate the dose. So I think it is adequately recognized.

But again, going too much on the other side is also a risk because that can lead to decreased use of this quite effective controller therapy. If you look at the U.S., it's approximately thought about that about half of the patients who should be on controller therapy actually are on controller therapy. If you look at Europe, it's actually much more high. So even in the U.S. with continued education, continued awareness, the use of controller therapy is not where I think where experts want. So in that context, putting too much of a cautionary note may actually lead the pendulum swinging in the opposite directions. This is a tight balance, and I mean you can give European and they like to hear that, but we think that balance is quite well struck.

MS. DOKKEN: Just one comment. I mean I think we talked a lot in the last two days about

that issue of balance. And I guess my own belief is that there may be a way to inform and empower families so that what I talked about yesterday, so that they are aware of the risks and can truly be part of the risk/benefit analysis. And I ultimately don't think that that will lead to panic, and you know, restricting use of medications from patients who need them. But I think it could lead to more informed decision making.

But also, families are part of the monitoring system, and if they're not always aware of what they're looking for, then they can't be very effective monitors.

DR. CHOWDHURY: It is a very good suggestion, and thank you for the suggestion, and we really take the suggestions very seriously from the public meetings. Just to let you know that when there are public advocacy groups and also family groups, one of them which is pretty active in the family field is Mothers of Asthmatics. And they're actually very much aware of what has been happening with the FDA. And many of those

meetings, they actually come, and they make presentations. So they are actually very much in line, and the persons who head up that group, we have lot of discussions with them, and as far as we could tell, they're pretty satisfied where the balance is right now, but again, your suggestion is very well taken, and thank you for that.

DR. CHESNEY: Dr. Fant and then Dr. Nelson.

DR. FANT: Just a couple of questions to fill in a couple of gaps on background for me. One, is there any data that points to--the decline in mortality has been commented on a couple of times. Does the data suggest that the use of the corticosteroids contributes to that, or--I'll let you answer that and then I'll just ask my second question after that.

DR. STARKE: The data on mortality comes from coding, primary coding for hospital discharge or death, and that's collected annually by the CDC. So this data, it's difficult to extrapolate any or interpret what the meaning of that data is compared

to the use of controller therapy. I don't think you can make any specific comments on the relationship.

DR. FANT: We know from studies that the use of corticosteroids is the most effective controller or one of the most effective controllers, but we don't know for sure if it is the major contributor to the decline in mortality; is that correct?

DR. STARKE: That's correct.

DR. CHOWDHURY: Let me make a comment here. I mean usually--I mean you can't really make a conclusion regarding an intervention and outcome which is mortality because in aspect it's still a very heavy event, so it's actually very, very difficult to make that conclusion. It's probably a combination of all. But if we take surrogates, for example, which is exacerbations of asthma, or hospitalizations because of asthma, which usually are surrogates of even worst outcomes, I mean usually with controller therapy all of these actually goes down, and I would not really pick out

one class of drug over the other as more contributing than the other.

DR. FANT: No, no. I'm not trying to pick out any. I'm just trying to get a better sense to help me sort of understand the complexity of this in weighing--

DR. CHOWDHURY: It is, and I think one can reasonably say--Dr. Starke mentioned that the better outcome that you're seeing is a combination of a lot of things, including better views of controller therapy. But other factors are also playing a role.

DR. FANT: My second question relates to Advair specifically and the adverse events that seem to be associated with that. Is there any data or information that looks at similar events that occurred when similar--the same two classes of drugs were used separately but in combination? Is it something that seems to be unique to Advair? Is it something that clearly seems to be an interaction between a long-acting beta agonist and steroids? Does it seem to be a beta agonist issue

only? Do we have any information that may help kind of provide hints and what may be the underlying problem, if there is one?

DR. CHOWDHURY: That's a very tricky question and maybe even a very tricky study to do, and the bottom line is the data is not available. And there are no studies long term looking at outcomes. What we have long term is the use of a beta agonist alone versus placebo, and you have probably heard about that study. But there is nothing such available comparing an Advair arm concomitantly taken, so that data is not there.

DR. FANT: Or adverse events that have been reported and in the narrative certain things get blamed, like--

DR. CHOWDHURY: Adverse events are there with fluticasone, adverse events are there with Advair, and as you have seen, with Advair the adverse events are just more, and they're higher, they're more serious. So that signal is there. But, I mean, there is no controlled studies that can go into the explanation whether it is from

Advair or whether it's something else confounding which is contributing to that. Those controlled studies are not available.

I don't think it really is a very useful information either because it's quite well known that Advair is taken by patients who are more sick and, therefore, having an adverse outcome coming out of a sicker patient population is not a big surprise, and also with the new beta agonist study we know that routine use of beta agonist leads to worsening asthma and increased death. And that's already in the product labeling for Salmeterol and also for Advair. So the information already is in a way known that routine use of beta agonist--

DR. FANT: But if you have a sicker patient who's getting treated with a drug that puts him at increased risk, if there's an interaction effect, that certainly is a patient I would really want to--really would not want to elevate that risk anymore.

DR. CHOWDHURY: Again, there is--

DR. FANT: You know, I'm not--

DR. CHOWDHURY: No, these are important discussions to have because it's actually quite important for, I think, everybody in the country to be aware of this. It is an increased risk of adverse outcome, but the risk is actually very, very small. If you look at the black box language which was put up very briefly, the number of deaths is like in two digits out of a 16,000 patient population. This is a very small signal. And I don't think really for the small signal one should not use the drug. The drug is very effective. There's no question about that. And it's also pretty safe. And the signal, which is a serious signal, is not very common. So I don't think--it is really, again, a balance. The signal is really coming out of a very small number of patients. And the more studies going through to the NIH initiatives trying to identify who those patients may be who actually would have the risk, that has been partly identified with the short-acting beta agonist. The studies which have been published--there's a large study which shows the biomarkers

associated with that. And in the future, there will be studies coming out trying to identify patients who are at risk.

DR. FANT: Thank you.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I'd just like to highlight two issues that are raised by the Flovent exclusivity studies, which I realize may be impossible to talk about today but might merit further conversation in the future.

One is the choice of control group. Those particular trials included children who had been receiving symptomatic treatment two times a week which meets NHLBI criteria for the provision of anti-inflammatory; but, nevertheless, a third of them were randomized to placebo. So the question would be: What is the current thinking about appropriate control groups when you have actually treatment guidelines that, in fact, a third of the population did not receive?

The second point is this was the study that also then had misallocation of study drug, and

so you end up with the irony--and they also were then granted exclusivity, and I don't know if that's because the written request was not ironclad enough to not give them exclusivity, or if, in fact, it was felt that they weren't to blame for the misallocation. But either way--and I realize each of these issues merit debate in their own right, but if you sequence them together in the most unfavorable light--which is not necessarily what I'm going to argue for, but some might--you have a study that withheld effective medication from a third of the kids in the study that didn't get done right, resulted in useless data, and they got the money anyway.

DR. CHOWDHURY: Let me take the questions very, very briefly, because you told it very correctly, these are really larger discussions.

The first issue is regarding placebo in these trials. There are two things to consider. They're actually placebo-controlled but not really without any drug treatment arm. These patients can take rescue medications as necessary and actually

can drop out of the studies if their asthma becomes uncontrolled.

The second thing is that in a short-term study taking off control therapy has not been shown to affect asthma in the longer term. There's CAM(?) studies out there going for quite some time, which does not show that if you do not use a control therapy for a short term, then the lung function of those children is reversibly damaged.

So there is some gain to obtained from some study, and withdrawing control therapy for a short time period with the proper rescue medications available is, again, a reasonable risk/benefit for the study.

And the second issue regarding, I would say, misallocation, whatever the reason being, of having drug in the placebo, is not something that I would--GSK did not want that to happen, neither did we, and the reason it happened is not really very clear. And you are totally right. Because of this, drug levels in the plasma, the studies were not useful. And whether exclusivity should have

been granted or not, I will defer to Dr. Murphy on that. It's a tricky issue.

DR. CHESNEY: Before Dianne comments, we may be looking at the same study. I can't tell. But Dr. Buckman's Slide 18, which was the--is that the same study?--where they found levels in the placebo and really couldn't come up with any conclusions at all, and your first thought is: Why was exclusivity granted when this study really on paper doesn't look very good?

Dianne?

DR. MURPHY: Between ShaAvhree and I, our memories are not clear enough to give you a factual answer. So we think it's because we weren't--you know, but one of the problems with exclusivity is that there's a short-term--we have to determine the exclusivity before the complete analysis is performed. And we will get back to you. I think this is one of the action items we need to get back to this committee at the next meeting about why was exclusivity granted in this situation. But our hazy combined recall--maybe Peter can help us. We

didn't know at this point.

DR. CHOWDHURY: Let me also chime in on this. The studies for pediatric exclusivity comes into a supplement to the NDA, and we have a time clock for reviewing the studies because it involves a lot of analysis, often going into the data and all, and the time frame is six months for pediatric studies. And exclusivity is granted or denied very early on.

DR. MURPHY: It's within 90 days, so--

DR. CHOWDHURY: So when the application comes in, we file the application, and then the exclusivity is granted based on whether the study was done fulfilling the criteria set forth in the written request. And the analysis goes on. So, I mean, one is happening before the other.

DR. MURPHY: What is determined, just again, for what we can tell you, is: Did they do the studies that we asked them to do? And so when the division comes to the Exclusivity Board, they bring the written request and basically a check item. They go through every item. Did they do 2,

randomize? You know, now, you could say it wasn't well controlled, but the division answers as best it can without having completed the analysis. And, therefore, the finding of some of these things, particularly some of the compliance issues and the scientific investigation issues are not available frequently until literally towards the end of the analysis.

DR. NELSON: Just a quick comment. I can appreciate the systems issues in my approach working in an ICU, this is all CQI systems issues. And if, in fact, it's the simple existence of a 3-month difference between one decision versus another and the data gets analyzed, then maybe we need to look at that as an issue. But I think certainly the intent of the exclusivity is to have interpretable data. And maybe there needs to be a fix. Whether that's a regulatory fix or a legislative fix--I realize you can't advocate for legislative fixes, but it just seems to me a gap that ought to be examined, and this would, in my mind, be a sentinel event. If I had something

happen in my ICU, we would look at it as a sentinel event and say, How do we close that gap?

DR. MURPHY: Actually, it used to be worse because we didn't have all of them on six months. And so the system was even more likely to have a problem, is what I was trying to say. We were hoping by having the six months versus the 90 days that we would have less events, but clearly we still have them.

DR. STARKE: Let me see--I'll try to answer the question as best as I can. I was the medical officer who reviewed the studies and presented to the Pediatric Exclusivity Board at the time. If I'm not mistaken--I'd have to go back and look, but I believe it was a 10-month clock for this that had preceded that. And the Pediatric Exclusivity Board met early in the analysis process. It was only later in the process that we found these events had occurred in the biopharmaceutical portion of the study.

DR. MURPHY: That's what I was referring to. Until the recent legislation, there were even

longer dates. Thanks for clarifying that.

DR. O'FALLON: Well, who is responsible for doing those biochemical, whatever, analyses? Is that supposed to be the investigator who put-- the company that gives it to you and you're supposed to look at it? Or is the FDA supposed to run it?

DR. CHOWDHURY: You're asking who is responsible for analysis of the results? It is the company or the company's contractor who is doing the study is supposed to do the analysis. And I'm pretty sure when the submission of the (?) was made, the company knew that there was some problem with placebo arms having active drug.

DR. O'FALLON: And they didn't share that information, they didn't give that to you?

DR. CHOWDHURY: It was there in the whole submission. That's the reason we know about it, and we did not approve the application. But if you go back to what was discussed earlier, the exclusivity determination is made very early on in the chronology of events. And in that time, that

formulation, that placebo had drug. I mean, it was not identified, and even if it was identified, you actually had to look at the cause of what happened and can still the study be salvaged anyway? And that takes time. And because of that, we have this six months versus ten months of clock to go through all of these. And by the time exclusivity is granted, it's basically based on was the study done based on what was asked. Analysis just cannot happen at that time because it requires time.

It is a system that, Dr. Nelson, as you pointed out, really as a--noting as a case.

DR. CHESNEY: The newest legislation is for six months, not 90 days anymore?

DR. MURPHY: No, for the review. All pediatric applications now are considered six-month reviews.

DR. CHESNEY: Any other questions or comments from the committee?

[No response.]

DR. CHESNEY: Let's turn to the question then which we have been asked specifically to

address. Based on the presentations you have heard today regarding drugs containing fluticasone or budesonide, do you have any concerns about the use of these drug products as labeled? If you do have concerns, could you please raise your hand?

[A show of hands.]

DR. CHESNEY: I believe with the members of the committee who are still here we have a consensus that we do not have any concerns about the use of these drug products as labeled based on the very comprehensive reviews you've presented to us.

x All right. Well, let me then just try to summarize what we have--the discussions we participated in this morning. The first had to do with the review of the Subpart D Pediatric Ethics Subcommittee summary, which was presented by Dr. Nelson, with some very good discussion by the committee. The committee had two additional recommendations for the summary, the first of which was to assure that no stimulants were provided within some reasonable period of time before the

study was initiated, and the second was that a comment be added to the consent form regarding the available NIMH information that only four of 3,000 patients who have had MRIs had any significant findings. Do I have that correct? Thank you.

Second, the committee understands that there will be no further reporting required for the four drug products presented mid-morning: ofloxacin, alendronate, fludarabine, and desloratadine.

The third point, there was significant discussion regarding adverse event reporting for drugs either approved or not approved for use in children, and I think not new to this particular committee hearing is the perception that we need better databases; particularly we need better databases that involve children. We also need better denominator data that involve children, and I don't think there was a lot of discussion reviewing the potential need for active surveillance for better documentation of adverse events.

And just to emphasize again the importance of having information from controlled clinical trials in order to better assess adverse events.

Finally, on the last issue with regard to budesonide and fluticasone, we were presented with very comprehensive data regarding the linear growth assessments, the HPA axis suppression, and regarding postmarketing adverse event reporting. And the committee--first of all, there was a recommendation that a MedGuide be provided for pediatric family caregivers with respect to the new labeling for Salmeterol and Advair label changes. And, secondly, a concern which was discussed in some detail today and yesterday, which I think overall we could say has to do with the quality of the studies requested for exclusivity, and I think we understand the process, but as Dr. Nelson pointed out, what we've come up against may be totally a process issue. And we understand better the reasons for why some of--why exclusivity is granted when the clinical trials may not necessarily seem to us to have been designed as

well as they might have and the results turn out not to be very helpful.

Any other summary comments that I have neglected with respect to the committee?

[No response.]

DR. CHESNEY: And, finally, in response to the specific question we were asked to address, we do not have concerns about the use of these drug products with respect to budesonide and fluticasone as currently labeled.

And, finally, just to thank particularly the FDA speakers who spoke this morning. I just have this fantasy that you rehearse these things for days and days beforehand and that somebody oversees them and tells you exactly when were going to have mental questions because you address them. At least as soon as they come in my mind, you address the issues. So we're just extremely grateful for how much you respect our time and for how comprehensively and well you review the topic. That is just very much appreciated.

Thank you also to Jan Johannessen, who has

done an incredible job of keeping everybody on track for the past week. This has certainly been a long trek, more so for you than for us for sure.

To thank all the panel members who are still here who raised always very stimulating and thoughtful questions from my perspective.

To thank Skip for chairing the first-ever Pediatric Ethics Subcommittee.

To thank Dianne, as always, for overseeing this whole operation; Solomon for his always comprehensive presentations.

And, finally, I think this is Dr. Ebert's last meeting and Dr. Maldonado's last meeting. Am I correct? And anybody else?

[No response.]

DR. CHESNEY: So I think they both got recognized at the June meeting of the old committee, but in any case, thank you from my perspective for coming back and joining us for this meeting and for being a part of this committee.

I'll let Dr. Murphy have a follow-up--oh, one more thing. Before we finish officially, I

wondered if the committee could stay for just one minute. We had suggested potentially at the June meeting writing up some of the--well, I'll address it right now--some of the issues that have come up over the years, and I am here to tell you that Dr. Laurel Leslie, who I understand in the pediatric community is known as a writing machine, has already written up a potential manuscript based on her review of what happened yesterday. And she's very interested in finalizing this and submitting it to a journal, and I would appreciate your thoughts, which we could do after we officially finish the meeting, as to who should be included in that, what journal you might consider that that should go into. She's thinking about Pediatrics, but I wonder, as we discussed in June, if there might be a more comprehensive audience if she thought about something like JAMA. But if you wouldn't mind at the end in a few minutes just giving me your thoughts about that, I would be very appreciative.

So, Dr. Murphy, to finalize?

DR. MURPHY: How many ways can I say thank you? That really ought to be the question. I know you guys have been--ladies and gentlemen, excuse me, have been through a grueling four or five days. I think what was interesting to hear this discussion this afternoon, which very much paralleled the questions that came up yesterday with the antidepressants where you have, you know, an adverse event that's part of the disease, if you will, and how you dissect that out and when do you not say the labeling is sufficient, because the division is certainly--they also do the labeling.

So I think it's a real compliment to you and the division that this committee, which has been trained, mandated, and working on labeling, you guys have done a good job. So I want to really comment. I wasn't sure what they'd say. Again, we look very much forward to the ongoing activities, and particularly, Dr. Nelson, to the immense amount of work that you put into condensing that entire day's ethical discussion and synthesizing it so well for this group that they had as few questions

and recommendations that they did, and the ones that they had were very thoughtful and very good. I just look forward to working with you guys in the future.

Thank you.

DR. CHESNEY: And is my understanding correct that our next meeting is a week from today? Is that--

[Laughter.]

DR. MURPHY: I wanted to say one last thing. Jan had no idea he was getting two committees. He thought he was getting one. And we are trying to make it so that you all don't have to have residences here in Washington, though I understand some universities do that. But we'll try to be reasonable in our future requests on your time.

Thank you.

[Whereupon, at 1:10 p.m., the meeting was adjourned.]

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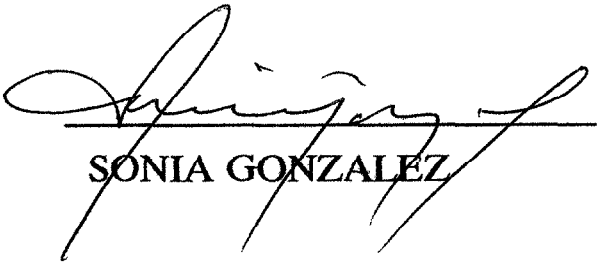

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