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.

C O N T E N T S

C O N T E N T S (Continued)

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