U.S. FOOD AND DRUG ADMINISTRATION

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OFFICE OF THE COMMISSIONER

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PEDIATRICS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,
JUNE 29, 2005

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The Advisory Committee met at 12:30 p.m. in Room 1066 of the Food and Drug Administration, 5630 Fishers Lane, Rockville, Maryland, Dr. Joan Chesney, Chair, presiding.

PRESENT:

P. JOAN CHESNEY, M.D., Chair
DENNIS M. BIER, M.D., Member
ANGELA DIAZ, M.D., M.P.H., Member
DEBORAH L. DOKKEN, MPA, Patient-Family Representative
MICHAEL E. FANT, M.D., Ph.D., Member
ELIZABETH A. GAROFALO, M.D., Industry Representative
MARY GLODE, M.D., Member
RICHARD L. GORMAN, M.D., Pediatric Health Organization Representative
PAULA KNUDSON, Acting Voting Consumer Representative
ROBERT M. NELSON, M.D., Ph.D., Acting Chair
THOMAS B. NEWMAN, M.D., M.P.H., Member
JUDITH R. O'FALLON, Ph.D., Member
VICTOR M. SANTANA, M.D., Member
ROBERT M. WARD, M.D., Voting Consultant
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

PRESENT FROM FDA:

SARA F. GOLDKIND, M.D., M.A.

SOLOMON IYASU, M.D., M.P.H.
LAWRENCE GRYLACK, M.D.
DIANNE MURPHY, M.D.
ROSEMARY ROBERTS, M.D.
ALAN M. SHAPIRO, M.D., Ph.D, FAAP
JEAN WENDY TEMECK, M.D., FAAP

PRESENT FROM OFFICE FOR HUMAN RESEARCH PROTECTIONS:
BERNARD A. SCHWETZ, D.V.M., Ph.D.

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(12:33 p.m.)

CHAIRPERSON CHESNEY: I think we're ready to start. Welcome to the Pediatric Advisory Committee and all of the members of the FDA who have worked so hard on the agenda from yesterday and for today and tomorrow. And I think we'll start with introductions and maybe we can start on my right.

DR. SCHWETZ: I'm Bernard Schwetz, the Director of the Office for Human Research Protections.

DR. IYASU: I'm Solomon Iyasu, I'm the Acting Deputy Director for Pediatric Drug Development of the FDA.

DR. GOLDKIND: I'm Sara Goldkind, the bioethicist in the Office of Pediatric Therapeutics.

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

MS. DOKKEN: I'm Deborah Dokken, the Family Representative on the committee.

DR. O'FALLON: Judith O'Fallon, Emeritus Professor of Biostatistics, Cancer Center Statistics of the Mayo Clinic.

DR. JOHANNESSEN: I'm Jan Johannessen. I am the Executive Secretary of the Pediatric Advisory Committee.

DR. CHESNEY: Dr. Chesney, Professor of Pediatric Infectious Diseases of the University of Tennessee and Director of the Office of Academic Programs at St. Jude.

DR. NELSON: Robert Nelson, Pediatric Critical Care Medicine at Children's Hospital Philadelphia and the University of Pennsylvania.

DR. GLODE: Mimi Glode, Professor of Pediatric Infectious Disease at Children's Hospital University of Colorado in Denver.

DR. DIAZ: Angela Diaz, Professor of Pediatrics, Mount Sinai School of Medicine, New York City.

DR. BIER: Dennis Bier from the Children's Nutrition Research Center at Baylor College of Medicine.

DR. FANT: Michael Fant, Immunotologist from the University of Texas Health Science Center in Houston.

DR. NEWMAN: Tom Newman, Professor of Epidemiology and Biostatistics and Pediatrics at UCSF.

DR. WARD: Bob Ward. I'm a Neonatologist and Director of the Pediatric Pharmacology Program at the University of Utah.

DR. KNUDSON: Paula Knudson, I'm the

Consumer Representative to the Committee and an IRB administrator at the University of Texas Health Science Center Houston.

DR. GORMAN: I'm Rich Gorman, a Pediatrician in private practice and a Pediatric Health Organization representative.

DR. GAROFALO: I'm Betsy Garofalo. I'm a Pediatric Neurologist. I am the industry representative. I work for Pfizer.

CHAIRPERSON CHESNEY: Thank you, and now Jan will read the meeting statement.

DR. JOHANNESSEN: I would just note for the record that Victor Santana will be participating in the meeting today. He's just running a little bit late but he will be here.

The following announcement addresses the issue of conflict of interest with respect to the first portion of this meeting and is made part of the public record to preclude even the appearance of such at the meeting. The topics of this portion of today's meeting are of broad applicability and, unlike issues before a committee in which particular products are discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been

screened for their interests as they may apply to the general topics at hand. The Food and Drug Administration has determined that no potential conflicts of interest exist. The FDA acknowledges there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated. We note that Dr. Robert Ward is participating in the meeting as a voting consultant and that Paula Knudson is participating as the acting voting consumer representative.

We would also like to note that Dr. Elizabeth Garofalo has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Garofalo is employed by Pfizer. In addition, Dr. Richard Gorman is participating as a Pediatric Health Organization representative, acting on behalf of the American Academy of Pediatrics. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on.

We have an open public hearing later this afternoon at 3:30 and I would just remind everyone to

please turn your microphones on when you speak so that the transcriber can pick everything up. Thank you.

CHAIRPERSON CHESNEY: Thank you, Jan. And now Dr. Dianne Murphy, who is Director of the Office of Pediatric Therapeutics, is going to give a brief meeting overview.

DR. MURPHY: While you were asleep last night, we changed the agenda, so we now have Dr. Goldkind, who will -- we try to let you know about these things a little before this, but I was so organized, I pulled it out of the book. So Dr. Sara Goldkind, who is a bioethicist in the Office of Pediatric Therapeutics is going to discuss the role of the Pediatric Advisory Committee and the Subpart D referrals and as you know, this meeting took place yesterday and Dr. Nelson will give us a summary after we hear from Dr. Goldkind.

DR. GOLDKIND: It's my pleasure to present to you some overview slides on the Subpart D referral process. Many of you will be familiar with this process but for those of you -- but it is confusing and so I want to go through it again. And for those of you who are not familiar with this, we also will welcome some questions after I'm done.

But yesterday we heard the deliberations

of this ?Precursor Preference in Surfactant Synthesis of Newborns? at the Pediatric Ethics Subcommittee meeting. It's the second joint referral since the establishment of the full Pediatric Advisory Committee and the Pediatric Ethics Subcommittee that we've done together with OHRP.

And what I wanted to go over is that now that the Pediatric Ethics Subcommittee has deliberated and established a set of recommendations that it's going to present -- that Skip will present to you today, the Pediatric Advisory Committee can review those recommendations and make -- and advance a set of recommendations to the Commissioner and the Secretary for consideration.

And those recommendations can be from one of the following. It can be a recommendation to allow the protocol to proceed because it satisfies one of the first three categories of Subpart D or it could be a recommendation to allow the protocol to proceed because it satisfies one of the first three subcategories of Subpart D with modifications. Or it could be a recommendation to allow the protocol to proceed with or without modifications because it would satisfy the fourth category of Subpart D, 46.407 or 50.54, which is indeed the category that the Pediatric

Ethics Subcommittee determined that the protocol would fit best in with modifications.

Or it could recommend that the protocol not be allowed to proceed and provide specific reasons for that recommendation. Now, as I mentioned, the Pediatric Ethics Subcommittee established that the protocol for the purposes of the comparison group should go forward under this particular category, and Skip will expand on this discussion.

But the three elements that have to be satisfied in order for this protocol to fit within this category are that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem effecting the health or welfare of children; that the research will be conducted in accordance with sound ethical principles; and that adequate provisions are made for soliciting the assent of children and permission of their parents or guardians as set forth in 46.408 and 50.55. And for this particular protocol, the assent of children is not applicable since we're -- the subjects are pre-term infants and full-term infants.

So we wanted to just underscore once again that although we have a different numerical system

with HHS, for the purposes of the Subpart D regulations, they are comparable, these four different categories.

Now, once the Pediatric Advisory Committee establishes its recommendation, that recommendation will be transmitted by the Office of Pediatric Therapeutics with comments on the recommendation to the FDA Commissioner for consideration. And not only will a letter from the Chair of the Pediatric Advisory Committee defining the recommendations of the Pediatric Advisory Committee accompany that transmittal memo but so will the summary that you have before you that was written by Dr. Nelson.

Then once the Commissioner makes a determination, that will be sent to OHRP, which will transmit that recommendation and it will be packaged with the Pediatric Advisory Committee recommendation and the Pediatric Ethics Subcommittee Chair summary for review by the Assistant Secretary for Health, who will make the determination for HHS on behalf of the Secretary.

So some of the possible determinations that are open to the Secretary or the Commissioner are that, again, similar to what are open to the Pediatric Advisory Committee, that in fact the research

satisfies one of the first three categories of Subpart D or that the research could be supported under the fourth category of Subpart D, 46.407 or 50.54, or that in order for it to be supported under 46.407 or 50.54, it would require additional modifications or not to support the research at all.

And additionally, the Secretary makes decisions related to funding, makes comments on funding issues, since this would be -- since there's an accompanying grant application to NHLBI or NHO -- right, NHLBI. And that's it. So if there are any questions or -- I'd be happy to take those now.

CHAIRPERSON CHESNEY: Are there any questions about the process?

DR. GOLDKIND: Okay, thank you.

CHAIRPERSON CHESNEY: Thank you. And now, Dr. Robert "Skip" Nelson is going to review the summary of yesterday's deliberations which, as Sara mentioned, you have in front of you.

DR. NELSON: Thank you. First, I would call people's attention to one of the handouts which was the handout we had available yesterday for our meeting, which has the title ?Pediatric Ethics Subcommittee of the Pediatric Advisory Committee.? The reason I think that may be of interest to some of

you is a lot of the information that we had to review this protocol was, in fact, not in the documents that had been originally presented but, in fact, in the presentations.

And I'd call your attention to Dr. Hamvas, the principal investigator's presentation starting on page 35 and then also noting page 43 where there is actually a hypothesis and the like. So, as I'm reading the summary, for those of you who are interested in his slides, that's where you'll find it.

And then I might suggest with the permission of the Chair, who is one of the people who was at open discussion at least, Paula, Michael and Joan have an opportunity to comment on my summary to make sure that I haven't omitted or misrepresented anything. So I'm going to just read this as people go along.

The Pediatric Ethics Subcommittee of the Pediatric Advisory Committee met on June 28th, 2005 to review a proposed research protocol entitled "Precursor Preference in Surfactant Synthesis of Newborns." The proposed research would be conducted at the St. Louis Children's Hospital and supported by the National Heart, Lung and Blood Institute.

The Washington University Medical Center

IRB referred the protocol for review under 45 CFR 46.407 -- and for simplicity throughout the rest of the document, I'll probably just list the last number of these references -- and 50.54 since it determined that the protocol is not approvable under 404, 405, and 406 or the comparable FDA 50.51, 52, 53, yet presents a reasonable opportunity to further the understanding of a serious problem affecting the health of children and could be conducted in accordance with sound ethical principles.

Now, the proposed research involves the administration of a 24-hour infusion of palmitate and acetate labeled with a stable (non-radioactive) isotope carbon 13, followed by the measurement of labeled surfactant obtained by routine, clinically indicated tracheal aspiration.

In addition, two to five blood samples totaling a maximum cumulative volume of 2.5 milliliters will be drawn from either an in-dwelling catheter placed for clinical indications or in association with a clinically indicated blood sample. In other words, there will be no additional procedures performed as part of this research protocol other than the 24-hour infusion.

All infants enrolled in the protocol will

have been intubated for clinical indications. There will be no catheters placed for the research, nor additional venipunctures performed as part of the research. As such, the incremental risks of the research beyond the risks of routine clinical care include the rare, defined as less than two percent risk of infection from the infusion, the possibility of glucose and/or electrolyte disturbances and the need for a blood transfusion given the additional blood volume taken for research testing.

During the presentation and discussion, the subcommittee heard data from 53 previously studied infants showing no increase in these adverse events when compared to protocol eligible but not enrolled infants.

The investigators have gone to great lengths to insure the safety of the 24-hour infusion. The subcommittee determined, in agreement with the referring IRB, that the risks of the research procedures presented only a minor increase over minimal risk. The protocol involves two different populations of infants who are intubated for clinical indications. The first population are infants born at a gestational age between 24 and 28 weeks who are studied shortly after birth at two weeks and four

weeks after birth. As of the continuing review report dated September 29th, 2004, 18 pre-term infants have been enrolled in the study. The Washington University Medical Center IRB approved the enrollment of the pre-term infants under 46.406.

The objective of this portion of the protocol was to study the surfactant production in pre-term infants suffering from hyaline membrane disease. As a study of the physiology of surfactant, the research did not offer the prospect of direct benefit to the individual infants enrolled. However, the risk was limited to a minor increase over minimal risk. The research procedures are reasonably commensurate with the experience of pre-term infants receiving clinical care for hyaline membrane disease and the pre-term infants have a disorder about which the research may yield generalizable knowledge of vital importance.

The second population are a comparison group of full term infants who require endotracheal intubation and mechanical ventilation along with the placement of intravascular catheters as part of routine clinical care for non-pulmonary conditions. To be included, these infants would need to have a normal chest x-ray and gas exchange as reflected in an

aspired oxygen concentration of less than 0.3. The investigators have proposed this population in order to explore the impact of gestational age versus the evolution of chronic lung disease on surfactant kinetics by studying a population of infants without lung disease. Although the ideal comparison group would be intubated and mechanically ventilated infants who are matched for both gestational and chronological age, such infants would be extremely rare.

It is the inclusion of this comparison group that resulted in the referral for federal review under 50.54 and 46.407, for these infants lack the disorder that is the stated objective of study, i.e. surfactant kinetics in pre-term infants with hyaline membrane disease. Although the Pediatric Ethics Subcommittee reviewed the amendment in the context of the entire protocol, it is the amendment to include this full term comparison population that is the focus of discussion.

The subcommittee reviewed the appropriateness of the comparison group drawing on the scientific presentations and expertise of the panel members. Although the protocol as submitted focused on the use of a full term population as a comparison group to shed light on the data from pre-term infants,

there are important questions of surfactant physiology and the respective impact of various disease processes and mechanical ventilation that could be usefully examined and would provide important information about this population of full term infants. Nonetheless, the full term infants in the comparison group lacked the condition as defined by the submitted protocol, in other words, disordered surfactant physiology as a result of prematurity.

The decision to study the intubated full term infants as a comparison group rather than the primary focus of investigation effectively defined this population as lacking the necessary condition under 406 and 50.53. However, the subcommittee believed that a protocol focused on describing surfactant kinetics in an intubated full term population of infants could have been approvable under 46.406 and 50.53. The subcommittee agreed that referral under 46.407 and 50.54 was appropriate for this protocol as written. The subcommittee also agreed that such referral may not have been necessary if understanding surfactant kinetics in full term infants who are intubated and mechanically ventilated had been the focus of investigation.

Following a full discussion of the issues

as reflected in the above summary, the subcommittee voted unanimously -- 11 in favor, no objections or abstentions -- in favor of the motion, approvable with conditions, under the Category 21 CFR 50.54 and 45 CFR 46.407. The subcommittee assessed that the proposed research presents a, quote, "reasonable opportunity to further the understanding of a serious problem affecting children, since premature births are increasing and have a high morbidity and mortality associated with them, such as an average hospitalization of two to three months and potentially significant developmental and medical sequelae.?

The subcommittee voted in favor of requiring two conditions for the research to go forward and of recommending but not requiring a third condition. The first required condition -- 11 in favor, no objections or abstentions -- focuses on the homogeneity of the comparison group in providing a meaningful comparison to the data generated from pre-term infants. The subcommittee discussed a number of conditions that may impact on surfactant physiology in full term infants, such as congenital abnormalities resulting in pulmonary hypoplasia and disorders in pulmonary blood flow associated with such conditions as congenital heart disease.

The subcommittee recognized that the principal investigator had listed some exclusions in his presentation. As the focus of the proposed research was not on describing the heterogeneity of surfactant physiology and the various conditions affecting full term infants, careful attention needs to be paid to make sure that this comparison group is relatively homogenous.

As mentioned, although the ideal comparison group would be intubated and mechanically ventilated infants who are matched for both gestation and chronological age, the subcommittee felt the proposed research would, in effect, be a descriptive, hypothesis-generating study and that inclusion of the comparison group would contribute to the overall knowledge potentially generated by the study. The subcommittee recognized that assuring homogeneity may involve a learning process as data about surfactant physiology in intubated full-term infants are obtained.

The second required condition -- 10 in favor, no objections, one abstention -- involves a number of modifications to the parental permission documents reviewed by the subcommittee, particularly the document intended for use in the full-term

population. The language needs to be simplified to an eighth grade reading level, including the required language about confidentiality and protected health information. The reference to there being no likely research-related risk should be deleted. The discussion of alternatives should be framed from the perspective of research participants and not from that of the investigators; in other words, the consent documents should mention that one alternative is not to participate in the research.

This discussion should also be highlighted under a section separate from the benefits of participation. The discussion of the purpose of the study should de-emphasize any immediate connection between the data arrived from full-term newborns and the understanding of the surfactant physiology in pre-term infants. The template language about not needing treatment found at the beginning of the document should be removed. Such language should not be included in the document describing a basic physiology study as it may inadvertently reinforce a therapeutic misperception.

Finally, there was considerable discussion about the importance of parents having an approachable and independent person to whom they can direct

questions about the research. Parents may be intimidated by the inclusion of titles such as, quote, "Chairman" and, quote, "Privacy Officer" in describing individuals who are available to answer questions about the research.

The third recommended but not required condition -- 11 in favor, no objections or abstentions -- continued the discussion of the importance of parental understanding of the research with the recommendation for an independent advocate to be available during the parental permission process; in other words, someone who would be approachable, accessible and available to discuss the research.

Although the subcommittee came to no conclusion about who such a person should be, there was general agreement about the function of such a person. A key function of such a person would be to assure that the parents, before signing the parental permission document, understood that this was a basic physiology study that offered no therapeutic benefit for the individual infant.

It should be noted that this recommendation was initially proposed as a mandatory condition but rejected as such by a majority of the subcommittee -- three in favor, eight against, no

abstentions.

In summary, the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee determined that the proposed research presents a reasonable opportunity to further the understanding of a serious problem affecting the health of children will be conducted in accordance with sound ethical principles and that adequate provisions are made for soliciting of -- we'll change that -- soliciting of the permission of parents or guardians as set forth in 45 CFR 46.408 and 21 CFR 50.55. As such, the Pediatric Ethics Subcommittee recommends that the Pediatric Advisory Committee recommend to the FDA Commissioner and the Secretary of HHS that the research be approved under 45 CFR 46.407 and 21 CFR 50.54 contingent on a satisfactory response to the two required conditions as discussed above.

CHAIRPERSON CHESNEY: Thank you. And Skip points out that the first of these subcommittee meetings he had four days to prepare the summary and this time he had less than 18 hours, so very complete. Are there -- is there discussion, questions, concerns regarding this summary? Dr. Bier?

DR. BIER: I'd just like to make a comment for the record about the independent, you know,

advocate. If this study is being carried out in an NIH clinical research center at Wash U., where there is a pediatric and adult center, all the GCRCs today have a staff, a program person who is either called a research subject advocate or medical director, and part of their role is to serve precisely as this kind of an independent, you know, voice, so I think they may have that person already.

DR. NELSON: They could choose to use that person but I don't think they have GCRC funding right now. So it wasn't -- as we asked, it wasn't part of their currently situation but that would be the person they could use.

DR. BIER: But there is a pediatric unit of the GCRC at Wash U. and they do do neonatal work.

CHAIRPERSON CHESNEY: Deborah Dokken?

MS. DOKKEN: I wanted to comment on -- as a family representative, I was really pleased to see the Condition 2 and 3 of the subcommittee because my own sense in looking at the background materials was having some questions about the consent document, not about the research itself.

For Condition 3, I guess I understand why this became -- was not left in as a mandatory condition, but it seems to me the independent advocate

is a mechanism for the underlying purpose of the insuring, as it says in the sentence above, parental understanding of the research and by making this not mandatory have, you know, have we sort of deflected the importance of insuring parental understanding. So is there a way of keeping in the parental understanding and not tying it to the mechanism of the independent advocate?

DR. NELSON: I guess my -- there was a lot of discussion with the principal investigator about the consent process, and at least speaking for myself, the first comment. The second comment, there was a broad discussion about the importance of that general issue and research in general.

And although there was some disagreement about whether this should be mandatory or not, I at least personally was relatively assured in listening to the principal investigator about how he would handle that conversation to where when it came down to say, "Well, what should we do in this instance, not in general," people felt comfortable that the process was a reasonable one and that parents were not -- were, in fact, being appropriately worked with. I mean, that was at least my take on the discussion of the process.

CHAIRPERSON CHESNEY: If I could just add a

couple of points. He was pointing out that they've been a leader in family center care, which I don't think I had fully appreciated, and he also pointed out that in the -- I think it's in the consent form, they say that we -- or I forget where, they talk to the family and then they come back 24 hours later and talk again, and if they're still not sure, then they come back 24 hours later. So I think that was some of the discussion that took place. Dr. Fant, do you remember any other --

DR. FANT: Yeah, just from personal experience situation, I know that I spent some time in St. Louis at that institution about, you know, I left about eight years ago. But the culture of the institution is one that takes sensitivity and respect of parents to heart. And as a matter of fact, I think the standard that's applied there is probably -- you know, I haven't seen it exceeded anywhere that I've been. So I personally am comfortable in this particular instance with this group of investigators implementing the principle of the recommendation for the purposes of this study.

In terms of my own comment yesterday, I think I specifically spoke to the point that while I was in support of the recommendation, I had concerns

about making it mandatory at this particular point in time, not because I have any concerns about the spirit of what we're trying to accomplish, it's just that if there are no clear ideas about who the person is, how their role is defined within the institution, you know, it may or may not fulfill the goal that we're all trying to achieve. So trying to make it institutionalized -- make something mandatory in my mind that's not defined very well, you know, doesn't accomplish a whole lot.

So that was the reason for my vote against yesterday, not voting against the principle of what we're talking about. And secondly, with this particular group, I had no reservations about the spirit of that recommendation being implemented.

CHAIRPERSON CHESNEY: Paula, did you want to make any comments?

DR. KNUDSON: No, I was just very glad that we had the discussion because I think it's terribly important to bring this up repeatedly that parents really in vulnerable situations need all the help they can get to make informed choices. So I was very pleased actually with the extent of the discussion and the final recommendation was fine with me.

CHAIRPERSON CHESNEY: I think if it's any

reassurance, it took up maybe not the majority of the meeting but close to it. Go ahead, Deborah.

MS. DOKKEN: I guess I wasn't clear. I have no question whatsoever about the particular institution because I know a fair amount about Dr. Cole's pioneer work in family-centered care in NICUs. And so I wasn't as much talking about the institution and the specific research as my own, you know, happiness that a statement like this was in a recommendation from this committee. And that's more what I was referring to, that I want to make sure that we don't soften what we say about the importance of parental understanding.

CHAIRPERSON CHESNEY: Dr. Newman?

DR. NEWMAN: Yeah, I have two concerns and a question. The first concern is in the materials here on page 15, the e-mail from Dr. Kalhan who says, "The committee is certainly aware of the case from Maryland when a contaminated solution of tracer palmitate/albumin was infused into a healthy adult resulting in septic shock, et cetera.? And so that concerns me and I'm thinking that if I were a parent, I would want to know that that had happened. That would scare me a lot, so I don't know how -- I have no idea what the denominator is for how many, you know,

palmitate albumin -- tracer palmitate/albumin solutions are infused but -- so this, I think, is scary.

My second concern is that the -- none of the stuff I read provided much of a scientific rationale for including the control group and how those data would be analyzed and how, you know, exploring surfactant synthesis in the control group would help understand what's going on with the babies they really want to study who have a problem with surfactant which the control group doesn't. So I just -- I didn't see how including this control group would further understand -- help further understanding of the condition in premies.

And my question is, it seems like there's two different standards and I'm not clear which one applies. One is a reasonable opportunity to further the understanding of a disease or condition. And the other is yield generalizable knowledge of vital importance. I don't think even in the premature group that I would think that this study would yield generalizable knowledge of vital importance.

I would say that it might contribute to the understanding of it. I don't even think it will contribute to much understanding including the control

group. So I'm not clear whether our standard is, you know, vital importance or contribute to understanding for both the pre-term babies and the term babies.

CHAIRPERSON CHESNEY: I'm just going to respond quickly and then let Skip pick it up and then I will. He said in his introductory comments that a lot of the material that convinced us to come to these conclusions was presented at the meeting and wasn't available and I have the exact same concerns that you did. I didn't understand the science of why was this so critical. And I have a much better understanding of that but I'll let Skip respond first. And I'm sure others who were there do also.

DR. NELSON: Tom, I think you're correct. The materials that were submitted before the meeting had nothing in it that would justify the scientific purpose, period, all right? So, you know, the bottom line, that's why I handed out the slides at least to give a representation of the information that was discussed and that took up the whole basically -- the majority of the meeting was all of that particular discussion and the issue surrounding those issues.

The interpretation of reasonable opportunity versus vital importance, I think, is an open question and we could debate from a regulatory

perspective whether they're meant to imply something different or not. I think from the discussion people felt that it met either standard and part of the difficulty was that this is an unknown area and to some extent that's what I was alluding to about the need to sort of start generating some of this data because you really can't do any kind of sample size without knowing the confidence interval around your point estimate. So basically, you sort of had to start doing it before you really knew do you need 10 or eight or 12 and that's, in a sense, the discussion of homogeneity versus heterogeneity was focused around some of those issues but without getting into statistical language.

And then on the final point, I actually disagree. I mean, we don't know anything about this anecdote. You know, if I put something together in my garage, yeah, it should be mentioned to the parents if they were doing it in their garage, but they're not doing that.

I mean, this is being prepared by Pharm.D.'s in laminar hoods in the same way that they prepare all of their other infused materials. And so I was reassured that the quality assurance, quality improvement, preparations that they do and a lot of

that was presented are, in fact, quite up to what I would consider an appropriate industry standard and not knowing anything about this anecdote other than this anecdote, I wouldn't want to -- I mean, that would be alarming for no particular purpose.

CHAIRPERSON CHESNEY: I have -- I'm torn. I want to hear from both of you but I wrote out a very brief paragraph based on what I finally understood of the science yesterday and I would be glad to share that or have your questions first.

Well, it turned out -- and again, Michael and Skip can -- and Dianne and other people who were there can correct me if I make a mistake, but it turns out the key slide is at the top of page 42 of yesterday's materials. And it turns out that if you give premature infants labeled acetate and palmitate, they pick it up and make surfactant. But what's the most interesting thing about this is the number of -- the amount of unlabeled surfactant which you can see decreases with time.

So the infant is using less either recycled or other surfactant and using almost exclusively the exogenously administered surfactant and that is, to me, the most intriguing aspect of all of this and it suggests that maybe their surfactant

pool is depleted. And that, therefore, leads to some other possibilities for therapy, one of which is that you increase the surfactant pool in some way.

And when I finally kind of understood all of this, I asked if anybody had considered giving surfactant to older premature infants. And it turns out that the NIH is, in fact, sponsoring such a trial right now. So I think that's another lead for possible therapy is that maybe this recycled pool, which appears to be decreasing with time, is actually being very rapidly catabolized in the premature infant. And if that's not the case in the normal infant, then that also opens up potential possibilities for therapy so you could understand -- if you could understand why the catabolism has increased.

And then their third and one of the most important issues, I think that Dr. Whitsett, who not only gave a presentation but then spoke in the open public hearing, had to do with nutrition, that we really have no idea how to nourish premature infants and should it be -- it is possible that we should be giving them a lot more palmitate or acetate, and so the whole issue of how this could impact how we peripherally nourish premies.

And the point as I understood it about using the newborns is that if you were to do the study in a newborn and, for example, discovered that the pool, the unlabeled pool, was the predominant source for surfactant synthesis in the newborn, then that's dramatically different than what we're seeing in prematures with time. So -- anyway, I'll let Skip correct or add to that.

DR. NELSON: I think that's a reasonable summary, I guess, from a non-surfactant physiologist's perspective, which is mine, too. I learned a lot.

DR. WARD: Joan, I would just say that I would agree with you completely about the importance of these types of studies to understanding how to better treat premies based on that analysis of this data.

I'd just like to respond to Tom's comment about the contaminated solution. If we were to react to every situation like that, every time we administered any dose that had been administered incorrectly in the hospital, we would have to go tell every parent that, "Yes, a tenfold digoxin overdose has killed a child but we're going to give this to your child because we feel they need it.? I just don't think we can respond to that in real terms and

in real world in providing care.

CHAIRPERSON CHESNEY: Dr. Newman?

DR. NEWMAN: The e-mail said the committee was certainly aware of that, so I figured that you knew something -- I mean, we know nothing about this case. We don't know whether it was part of, you know, a human subjects approved protocol, it was research or anything about how it happened because I think actually it might be good to know about it because maybe it was a human subject's approved protocol that had all of the same safeguards that are being described here. I mean, I don't know, so I just -- that concerned me.

CHAIRPERSON CHESNEY: Dr. Goldkind?

DR. GOLDKIND: I'm not certain that the case that I'm thinking of is the case that's referenced in this comment. I was suspecting that the person was referring to the Johns Hopkins University 19-year old who was enrolled in an asthma trial who was administered a shelf chemical. There were questions about how that was prepared and she had an acute asthmatic attack and was unable to be resuscitated.

DR. NEWMAN: This says septic shock from a tagged palmitate, so it sounds much more close to this

drug test.

DR. NELSON: All that is is antitoxin and basically all you need is quality control to make sure there's not antitoxin in the solution. And I've seen that happen when people are getting bone marrow transplants. You know, so even if the anecdote was within research, I don't think it -- with their presentation of what they've already done to date, this is based on, I don't know, eight years of doing this work and dozens and dozens of preparations, et cetera. I don't think it's applicable, even if we knew more detail.

CHAIRPERSON CHESNEY: They also pointed out that it's -- and the neonatologist could confirm this -- that albumin is hung for 24-hour periods of time in the neonatal nursery every day and infection is not of concern any more than the sort of low-level constant.

Any other -- Dr. Ward?

DR. WARD: I would just make one observation about this issue of having the advocate there for the parents. Every time we develop an informed consent relationship with a family, it's always incumbent on us to be sure to the best of our ability that the parent fully understands or we do exactly what they describe of coming back another time

and if they ultimately don't understand exactly what's happening, they can't participate -- their child can't participate. This seems to me like double coverage and I think that's commendable, especially in this particular patient population to be studied.

CHAIRPERSON CHESNEY: Dr. Nelson?

DR. NELSON: I would like to just highlight the issue that I raised in one of the paragraphs just to reinforce that point because it took a fair amount of discussion for me to sort of wrap my mind about that and that's the paragraph on page 2 that starts, "The subcommittee reviewed the appropriateness of the comparison group.? In effect, what this trades on is the ambiguity of the word "condition" within the regulations.

These investigators presented this comparison group which, A, they're not normal. They are diseased newborns, they just are thought not to have a disease that impacts on surfactant physiology. So they presented them as a diseased comparison group and therefore, in that way, that group did not have a condition that was the focus of that investigation, but the risk was felt to be a very minor increase over minimal risk.

Now, had the investigators actually

proposed to study the impact of even mechanical ventilation on surfactant physiology, which, as an ICU doc, I know it can impact, this would not have even come to a 407, 50.54 review. It could have been approved under the category minor increase over minimal risk, et cetera. So that's what I'm eluding to here. As written, we recognized it was an appropriate referral. Had they said that the condition they were investigating was the impact on surfactant physiology of these very same diseases that these newborns had that they were then offering as a comparison group, it is possible, speculative but possible, that the IRB locally could have approved it under the minor increase over minimal risk under 45 CRF 46 and 50.53. So just to -- I think that is worth at least highlighting for people's information and edification.

CHAIRPERSON CHESNEY: Just to amplify that, Dr. Fleischman said right at the end of our meeting that had that word "condition" been worded slightly differently, just what Skip said, the whole issue never would have come before the committee yesterday because it was a lot of time, effort and manpower for what, as Skip says, was considered a relatively minor increase over a minimal risk. So it was an

interesting exercise.

Any comments from the FDA with respect to this?

DR. MURPHY: I think the committee is asking all the appropriate questions because this is actually where the discussion went yesterday. There was a tremendous amount of time about the concern, about how is this control group going to relate back to this premie group? Well, you know, not really. And how do we better define the control groups and how useful the information just out of the control group would be by itself.

Also, I think there was some discussion, and correct me if I'm remembering this, because I didn't bring my notes from yesterday with me, is that the discussion of the additional risk of infection from the infusion was considered by the IRB, you know, was noted as one of the things and was looked at and investigated as to, you know, what is that risk and what do we think it is in our institution. And I think that that all was put together in their thinking about how they referred it, and I think it came down to that really the risk here is the infusion in the blood, you know, the extra blood, and that that infusion is going to not be an additional line, so

you're not, you know, don't have an additional line sepsis site and that it really gets back to what everybody has described as this minor increase. So I do think that the discussion is really going pretty much where, I think, a lot of the concerns were yesterday, and unfortunately we just didn't have all of the science information slides to provide you all until we got them and the committee got to see them yesterday.

CHAIRPERSON CHESNEY: I assume that we need to take a vote on this, and Dr. Nelson, do we need -- can we take one vote or do you think we ought to vote on each of the conditions? Or how --

DR. MURPHY: Joan, you know, last time you all -- if the committee had recommendations that it felt strongly about, you know, we did take those and put those into our referral, so I think the opportunity of this committee, like yesterday, has recommendations that you all need to discuss, I guess is what I would put on the table, as you go around.

CHAIRPERSON CHESNEY: Right, additional recommendations. All right, should we go around and do it person by person and then people can say they approve of everything as stated or have an additional recommendation to propose? Okay, let's start here

with Dr. Garofalo.

DR. GAROFALO: I don't have any additional comments and I'm not certain if I'm a voting member for this portion but I certainly approve -- agree with the recommendations.

CHAIRPERSON CHESNEY: Thank you. Dr. Gorman?

DR. GORMAN: No additional recommendations but an observation that this is the second such meeting, and while the bugs and kinks are still being worked out, it's the second time that at the meeting substantial additional data was presented that was not available to the review committee prior to the meeting and perhaps, in our due diligence as we move forward with this process, that that can be rectified.

DR. KNUDSON: I have no additional recommendations. I suggest that we accept the report as outlined by Dr. Nelson. Thank you.

CHAIRPERSON CHESNEY: Thank you. Dr. Ward?

DR. WARD: I would recommend that we accept the report as Dr. Nelson submitted it.

CHAIRPERSON CHESNEY: Dr. Newman?

DR. NEWMAN: I think I'll abstain on that. I'll agree with Dr. Gorman. At least for me, it's -- I'm used to sort of reading stuff and having time to

think about it and so I don't feel like I can, you know, meaningfully vote on this because, although what Joan said was clear and made sense, it's just hard for me to absorb it, you know, in a few minutes, and so I still don't understand the scientific value of the control group, so I'll abstain.

CHAIRPERSON CHESNEY: Dr. Fant?

DR. FANT: I vote to accept the recommendations as outlined.

CHAIRPERSON CHESNEY: Dr. Bier?

DR. BIER: I vote for the recommendations as outlined.

DR. DIAZ: I vote to accept as outlined.

CHAIRPERSON CHESNEY: Thank you, Dr. Diaz. Dr. Glode?

DR. GLODE: I'd like to abstain. I realized yesterday that I have a personal relationship with a relative of the principal investigator that I didn't realize until yesterday, so it would be in my best interest to abstain.

CHAIRPERSON CHESNEY: Dr. Nelson?

DR. NELSON: I guess it would be odd if I made any changes. I don't have any further changes to recommend.

CHAIRPERSON CHESNEY: Go ahead.

DR. NELSON: No, I don't. I stand.

CHAIRPERSON CHESNEY: I accept the recommendations as summarized. Dr. Santana?

DR. SANTANA: I have no additional recommendations, and beyond accepting, I would endorse the recommendations because they are very appropriate given the issues that were presented in the subcommittee.

CHAIRPERSON CHESNEY: Dr. O'Fallon?

DR. O'FALLON: I accept as stated.

CHAIRPERSON CHESNEY: Deborah Dokken?

MS. DOKKEN: I also accept the recommendations of the subcommittee.

CHAIRPERSON CHESNEY: Thank you. So, Jan, we have two abstentions and --

DR. BIER: Joan, could I add something?

CHAIRPERSON CHESNEY: -- and 10 yeses. Yes, Dr. Bier.

DR. BIER: Just for the record, I spent 19 years at Washington University. I know all the principals there, just so we have it in the record.

CHAIRPERSON CHESNEY: Thank you. I can't even think of a quick response to that. Is there anybody here who hasn't spent time at Wash U. in the nursery?

(Dr. O'Fallon and Dr. Santana raise hands.)

CHAIRPERSON CHESNEY: That speaks well for their nursery. Do we need any further discussion on this issue from the OHRP's perspective? Dr. Goldkind?

DR. GOLDKIND: Thank you very much and we will take those recommendations into account as we continue to try and tease -- hone the process. We've instituted, as the subcommittee noticed yesterday, a number of changes that made the protocol and the consent documents much more of the focus of the discussions than they were in the first subcommittee meeting, which had, you know, a number of inconsistencies that were brought to the attention of the IRB chair and the PI at the subcommittee meeting. So we will try and be able to get all meeting materials -- set, perhaps, a due date for all meeting materials so that they can be supplied to both the Pediatric Ethics subcommittee and the Advisory Committee in advance of the meetings.

CHAIRPERSON CHESNEY: I would support that suggestion because I think it was as confusing for you all as it was for us until we heard the material yesterday.

Shall we proceed with Dr. Murphy's

presentation or is there a reason to wait until two o'clock? Okay, our next speaker is Dr. Dianne Murphy, as previously introduced, Director of the Office of Pediatric Therapeutics, who is going to give an overview of the Advisory Committee activities.

DR. MURPHY: As you can tell, we've had a change in agenda, and fortunately it fit with some of the activities that we wish to accomplish today anyway.

A year ago, we had the dissolution of the Pediatric Advisory Subcommittee of the Anti-Infectives Committee and the formation of the full Pediatric Advisory Committee and I thought -- it's been suggested that it might be a good idea annually for this committee to have some idea of what's been going on and to review what has been happening.

In addition, at the end of this meeting, we will lose three members of our committee. So I wanted to take a few moments and review for everybody sort of where we've been and where we're going. And what do I do -- you'll do it for me? Okay.

So there have been rather a number of changes and some of them fairly large since we began on this road in 1999. And that's when we had our first Pediatric Advisory Subcommittee meeting. And we

right out of the chute began dealing with both scientific and ethical issues. And ethics was such a big component of some of our first meetings that we actually developed a cadre. We had six different ethicists or more at the time that we had as SGEs that we were calling on on a fairly regular basis to help us with these questions and issues that arose.

Because we were already a subcommittee, we couldn't have an ethics sub-subcommittee, so we -- I couldn't come up with any other better terminology than the cadre of ethicists. I mean, somebody else can think of a better term, an expert group would be -- of ethicist. Next please. I'm sorry, and then we did become a full, after BPCA, become a full Pediatric Advisory Committee in 2004, as I mentioned, and that we were able to form, then, an Ethics Subcommittee which has now been very busy also, not only with the Subpart D referrals that they get but also with some other ethical issues that are coming their way.

And then recently, we asked you to advise us. The committee had already been participating in a number of reviews of products, safety assessments, the one-year, post-exclusivity safety assessments, and we asked you to provide us some feedback on how to make that process more useful to you where we could. And

actually, today and tomorrow will be our first attempt, and you'll see that despite our deliberations, things didn't fit into all these categories but we'll continue to refine it. So that is, I think, another important step that we are taking in our progress of trying to make the work of this committee efficient and productive and useful and meaningful to you because, as you'll see, it's a huge amount of work that this committee has been performing. Next slide, Jan?

Just real quickly because I promised I would not spend a whole lot of time that we have time, so I mean, is that okay, Solomon, if I take a little longer now? They tell me I am always over, spend too much time talking but there -- we had at least the three ethical issues that came up very early in our deliberations. These are big issues, you know, the pediatric trials, the use of subjects versus patients. I can tell you it's still an ongoing issue, the placebo control trials when can -- when they occur. And then we had a particular product which was needed to be studied in a very vulnerable pediatric population; how do you approach that? And actually many of the discussions we've had come up time and time again about the involvement of -- and

particularly in these vulnerable populations, not only the parents but also many of the caretakers who have so much insight as to what's going on with this population. So next slide, please.

And our two Subpart D referrals that we have now complete the process. We've had a number of other, I don't want to say inquiries but let's put them in that category, that have not completed the process but need to. Next please.

Very quickly, I'm going to resummarize for you of all all of the science issues that you have addressed since -- many of you have addressed since 1999. This first discussion was both an ethical and science, which often we are finding occur. Should we even develop a product for insomnia for kids? So it was both what are the scientific needs, what is the rationale and what are the ethical issues. The issues of developing psychotropic products for children and the treatment of chronic Hepatitis C. Keep going, Jan, we'll try to go through these quickly.

The next three meetings involved the development of antiretroviral drugs in HIV-infected and exposed neonates. And what -- had we had enough research in this area, what else was needed? And then the next one was the current epidemiology and

therapeutic interventions relevant to hyberbilirubinemia. This is a field that is -- how should it be developed? How should we move forward? Tremendous potential impact. And then the -- how do we develop trials for reflux and GERD when the approach that's used for adults is very different than what's used for children. Next.

Then in February of 2004, the use of imaging drugs in conjunction with cardiac imaging procedures in the pediatric population, how do we move forward in that area, and of course, the beginning, the first of two meetings concerning suicidality and clinical trials for antidepressants for the pediatric population and at that meeting, the issues were defined and the approach. Next, please.

And in October of 2003, we talked about what are some of the clinical risks and brought this committee -- you know, what sort of messages should we be providing to the public when we don't have a known or defined risk but a potential risk both with the HPA axis suppression with the topical corticosteroids and then a very detailed discussion on how do we try to define studies to identify potential cancer risks. Next, please.

We had an update for you all in 2004, as I

mentioned at our final subcommittee meeting, which came out of a prior meeting in a safety review meeting that this committee had where you wanted more information on the neonatal withdrawal syndrome that was being seen with the SSRIs.

And in September of 2004 was the second meeting involving suicidality in the clinical trials for antidepressant drugs for pediatric patients. As you'll note, a number of these committee meetings have been combined committee meetings, not just with this committee but with Neuro/Pharm. They seemed to be our frequent partner in a number of these but also with the GI Division and Dermatology Division. Next, please.

And then the discussion I just mentioned that we had on how to improve reporting and this past February, the discussion we had on potential cancer risks in children and the use of topical calcineurin inhibitors and, next, would be to our meetings now.

I'm going to not go through every one of these. I'm going to ask Jan to just flip through these so you can see the dates, the breadth of the topics, bring you up to 2005, keep going and this is where we are today. As the number of products this committee has looked at the adverse reports on. Next,

please.

To summarize it, the Pediatric Advisory Panels, including both the subcommittee and the full committee, have met to discuss ethical or scientific discussions 19 times since 1999. These panels have also had seven sessions devoted to safety, review of safety products, and you have reviewed -- as of tomorrow, you will have completed 42 products that have been reviewed. We will continue. We have a long list still to go and we are implementing your changes that you requested and we will continue to provide you all the written material as soon as we get it.

We're going to try to get it earlier as clearly has been indicated, and I've just listed here for you the things that we will always continue to provide you, which are the Office of Drug Safety adverse events reports and the use reports, the exclusivity studies, the Pediatric Division slides and the labeling. Next, please.

We will provide you an extensive assessment of products with possible new or increased safety signals as we will be doing tomorrow and this may include additional information from other experts outside of FDA. And we will provide a brief oral summary for the committee on products with no new or

less concerning safety signals and will state why we've come to that conclusion that was with the committee. Next, please.

But as I said, we're going to -- we're finding already that everything doesn't always fit into those categories and we actually have come up -- I think the terminology as we've got our extended reviews, our standard reviews and our abbreviated reviews, something along that line now that we're going to be providing for you. Next, please.

I wanted to say to everyone, this is a pretty amazing record, the number of topics that you all have looked at, the number of products that you reviewed. I think a lot of recommendations have come out of these meetings and we want to thank you very much. For those of you who will not be leaving the committee, there is much more to come. We have a number of public health issues that we will be bringing to you and some more issues concerning ethical trial design that is scientifically and ethically consistent with where we want to go.

So that's my quick overview of where we have been and where we are going. And I just want to take this opportunity to say thank you and goodbye to three of our members that are leaving us. We would

like -- Dr. Victor Santana, the Food and Drug Administration would like to provide an Advisory Committee Service Award in recognition of your distinguished service to the people of the United States of America. Thank you very much.

(Applause)

DR. SANTANA: Thank you. May I say a few words?

DR. MURPHY: Oh, please.

DR. SANTANA: Actually, it's a very humbling experience to have been asked to serve on this committee and certainly bring some of my expertise in hematology and oncology, but more important, what I've learned is how sensitive the FDA has become in the last few years to these pediatric issues. And I want to encourage the agency to maintain those high standards and being sensitive to the issues that we have to deal with. Thank you.

DR. MURPHY: Thank you. Okay, Dr. Glode, if you would please come up also. I always love the wording on this things. Again, the U.S. Food and Drug Administration Advisory Committee Service Award is being presented to Dr. Glode in recognition of distinguished service to the people of the United States of America. Thank you very much, Mimi.

(Applause)

DR. GLODE: Thanks very much. I also feel that I have undoubtedly gained as much as I've given, especially on this committee that has such a broad range, and so it's been a very educational experience. Thank you very much.

DR. MURPHY: And now to the individual who has been the mother of the Pediatric Advisory Subcommittee and Committee, I wish Dr. Joan Chesney please come up and let us tell her -- and not only does the Food and Drug Administration want to thank her, but also to comment on the wonderful leadership that she has provided as the Chair of this committee and that not only has she provided wonderful, scientifically sound leadership but she has been fair and gracious and I think they will be shoes that will be hard to fill. And I want to personally also thank her for this wonderful contribution to FDA, Joan.

(Applause)

CHAIRPERSON CHESNEY: Well, I was reminiscing with Skip yesterday about -- excuse me, as you know, I get too emotional. It's much easier to discuss science -- reminiscing about the most difficult meetings and perhaps the most rewarding and I don't know how many of you were involved in the GI

Committee on reflux. How many of you were on that one? That had to be the worst. It was a situation, for those of you who weren't there, where the gastroenterologists were sitting here and the neonatologists were here and they -- one group said reflux didn't exist and the other said it did and there was no agreement about whether it existed and trying to go forward from that was difficult.

Two other things. I think the lowest point of my tenure on this committee was the time I climbed into bed with a bug at the old Ramada Inn when we were still being put up there. One of the highest moments was Jan and Stan and their van service. That has just been a tremendous asset because you probably know that when you have a six o'clock plane and the meeting is going till four or five, you're antsy from one o'clock on, and that's just made a huge difference.

And what was the last thing that I was going to comment on? Well, I can't remember it right now but anyway, thank you all. This has been tremendously rewarding and we really don't even do the work. It's the FDA that does all the work and it's just been a tremendously rewarding experience and I'll stop there. Thank you.

DR. NELSON: Joan, do you mind staying up

there for a quick second?

DR. MURPHY: Skip has a --

DR. NELSON: I shared with a couple people on the committee that you'd be stepping out before the end of the meeting and Dr. Gorman penned some words that, having read them, I think, share my sentiment and I hope the sentiment of the rest of the committee. So I'm just going to read them.

"Since 1999 Dr. Joan Chesney has led the committee with expertise, wisdom and grace. In fact, she's been the only chair of both the subcommittee and the committee to date. She has led, refereed and summarized discussions and what discussions they have been: epidemiology, basic science, clinical trials, ethics, open public hearings that often presented hard-rendering personal experiences, and, of course, attempting to give coherent answers to questions posed by the Food and Drug Administration.

?During all this time, Dr. Chesney treated all participants with respect as an active listener and as a chairperson reaching out to allow each individual to bring their insights, knowledge and point of view to the group. Her steady hand on the tiller has led to balanced discussions and thoughtful decision-making. Thank you, Dr. Chesney, for your

service to the FDA. As a result of your work as the Chair of this committee, the health care of all children in the United States has benefitted. We wish you good luck and much success in all your future endeavors.

CHAIRPERSON CHESNEY: Thank you, thank you, Dr. Gorman, thank you everybody and I remember the last thing. Thus ended the St. Jude reign on the Pediatric Advisory Committee.

DR. MURPHY: Okay, I think we're scheduled for a break. Is that correct? We're a little early, so -- okay, we will reconvene at 2:15. Is that what you're saying, Jan? Okay, thank you very much.

(Whereupon, at 2:15 p.m., short recess was taken.)

DR. NELSON: So if we could get started. For those of you who haven't noticed, I'm not Joan. Joan decided to recuse herself rather than divorce her husband. We should all be so lucky. Anyway, So we have a reading of the opening statement.

DR. JOHANNESSEN: Thank you and good afternoon. The following announcement addresses the interest of conflict of interest with regard to this portion of the meeting and the discussion of a report by the agency on adverse event reporting as mandated

in Section 17 of the Best Pharmaceuticals for Children Act for Ortho Tri-Cyclen Cipro, Detrol La, Arava, Zemplar, Zlomig and Trusopt 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 interest 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 USC 208(b)(3) full waivers have been granted to the following participants; Dr. Dennis Bier, for ownership of stock in a company with a product at issue valued between 15,000 and $100,000.00 and stock ownership of a company with a product at issue valued at less than $15,000.00 and Dr. Robert Ward for a contract between his institution and a company with a competing product with a total value of less than $100,000.00.

We also note that Dr. Victor Santana reported stock ownership in a company with a competing product below the diminimus value of $5,000.00. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parkland

Building. In the event that the discussions involve any other products or firms 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 note that Dr. Robert Ward is participating in the meeting as a voting consultant and that Paula Knudson is participating as the acting voting consumer representative. We would also like to note that Dr. Elizabeth Garofalo has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Garofalo is employed by Pfizer. Dr. Richard Gorman is participating as a pediatric health organization representative, acting on behalf of the American Academy of Pediatrics. With respect to all other participants, we ask in the interest of fairness, that they address any current or previous financial involvement with any firms whose product they may wish to comment on.

We have open public comment scheduled for 3:30 and I would just remind everyone to turn their microphones on when you speak. Thank you.

DR. NELSON: Thank you. So the first item

on the agenda is an overview of the agenda and the committee's role in BPCA safety reviews. That's going to be presented by Dr. Solomon Iyasu who is the Acting Deputy Director for the Division of Pediatric Drug Development. He's trained in pediatrics and medical epidemiology. Solomon joined the FDA in 2002. Prior to that he served as a medical team leader in the infant health program of the CDC. Solomon.

DR. IYASU: Thank you very much. It's my pleasure to welcome you today. We've now come to the adverse event reporting part of this meeting. I'm going to just provide an overview of the agenda and also describe to you the role that the legislation has provided for the committee members in this review. As you know, the Best Pharmaceuticals for Children Act was signed into law January 4, 2002. And this was authorized in 1997 in FDAMA and reauthorized in BPCA with respect to the provision of an incentive program providing exclusivity to drugs that are studied in pediatric patients.

The provision under this BPCA for exclusivity sunsets in 2007 so today the adverse event reporting is really mandated by the law to be provided for drugs that have been given exclusivity under this law. Just to give you a little overview of how

exclusivity process is defined at FDA and how it's defined by the law, the origin of these studies in pediatric patients starts with the background literature, extensive literature review and background research to determine if there is a need for a study for a particular condition in a pediatric population. The request for studies could be generated either because the sponsor has proposed a pediatric study or a PPSR as a quote and FDA determines that this is an important -- there's an important public health issue that needed to be addressed, then the FDA will issue a written request to a sponsor.

Sometimes the written request may be originating from the FDA because there's a public health need. The written request that is developed by the Review Division may be -- is actually reviewed by the Pediatric Implementation Team at the FDA and once that is approved the written request is issued to the sponsor and the sponsor, if it accepts the written request may complete the studies then submit them for determination of exclusivity. Exclusivity determination is done by the Exclusivity Board at FDA. It has to be done within 60 to 90 days after submission of the studies.

And exclusivity is given to a sponsor if

it has fairly met the specifications as written in the written request and that the data that are collected under the studies are done in the manner specified in the original request. They do not have to prove that there's efficacy or that the indication is -- for the indication for which the drug is studied. And actually an application might take several months, six or 10 months but exclusivity determination is done within that time frame.

Now coming to the legislative mandate for doing these reviews and why we are here today, the BPCA specifies under Section 17 of the Act that the Office of Pediatric Therapeutics would review postmarketing adverse event reports during the one-year period after drug receives market exclusivity and the law also requires that such reports are referred to the Pediatric Advisory Committee for review in obtaining any recommendations for action. And therefore, that's the main reason why we're here today.

Now to review for you what data systems we use to be able to do these BPCA reviews. We mainly use the data base of all MedWatch and manufacturers' reports which is the AERS system. As you know, this started in 1969. So far there are about two million

reports that have been accumulated in the system and may contain drug adverse event reports for therapeutic and biologic reports. This system, the AERS system excludes, of course, the vaccines which is tracked under a separate surveillance system called VAERS.

The sources of these reports, the Adverse Event Reports are mostly voluntary or spontaneous reporting. They are reported usually by health care professionals, consumers, patients or others but a large proportion of these reports come in because, they're required part of the reporting for manufacturers and all adverse drug experience information obtained or otherwise received from any source, foreign or domestic is a requirement for the sponsors to report to the FDA.

Now, just to give you a little background again on the FDA postmarketing definitions, which are defined actually under 21 CFR 314.80, the Adverse Drug Experience or ADE is any adverse event associated with the use of a drug whether or not considered drug related or not, including accident or intentional overdose occurring from abuse or drug withdrawal or failure of expected pharmacologic action.

Again to review the postmarketing definition, what is an unexpected ADE or unlabeled

adverse drug experience? It is defined as any event not listed in the current labeling for the drug product including events that may be symptomatically or pathophysiologically related to labeled event but differ because of greater severity or specificity. And this may be relevant to the discussion tomorrow so I mentioned it here. Then again, another definition that we all need to be on the same page, there's also a definition for what a serious adverse event is. And that's defined as any event occurring of any drug as a result of any of the following outcomes. It could be a death, life-threatening event, hospitalization for a significant disability or a congenital anomaly or birth defect or other events requiring intervention.

Now, just to give you a little overview of how we assess some of these reports that we receive, an important consideration is, of course, making -- evaluating the temporal relationship between an event and a drug that is taken by a particular patient. And also look for issues related to de-challenge where an ADR or event the signs and symptoms subside when the drug is discontinued. We also look for any evidence of rechallenge where the signs and symptoms are reported may be re-emerging again upon readministration of the drug. We look for dose

response relationship because that would give us some idea of what relationships there might be between the drug use and a reported adverse event.

We also take into consideration biological plausibility and available knowledge of PK and PD about the medications that are under surveillance. Other issues that we consider, animal preclinical studies, laboratory evidence, known classified and also looking for alternative explanations for why that event may occur related to maybe this is a manifestation of an underlying disease or is related to concomitant drug use. Just briefly, you know, we've provided this information to you before but it's, I think, useful to say a few words about the strengths and limitations of the AERS system. This basically includes all the U.S. marketed drugs, simple expensive reporting system, inexpensive reporting system. I think one of the useful attributes of this system is that it's good for detecting rare and serious adverse reactions but for commonly occurring or more frequent events it may be not that sensitive.

Limitations, again, it varies from drug to drug in terms of reporting but generally, there's a significant under-reporting events to the system and there's variability in terms of the quality and

completeness of records that we'll see. And another big, I guess, limitation is that the numerator is very -- is uncertain in terms of the number of counts that we have because it's sort of a sample of what the population of events maybe have been occurring in a population. The denominator is usually estimated. We don't have a good handle on denominators, so it's difficult to assess risk or measure risk or quantify risk.

Now, coming to the role of the committee, as I specified in my first slide, the role of the committee is actually defined in the law. That they would have to -- they would focus on the review of the one-year post-exclusivity adverse event and we have decided to provide, as usual, additional information that will provide the context in which to evaluate some of these reports and this includes the drug use reviews which are prepared by the Office of Drug Safety and the summaries of the clinical and pharmacology/toxicology reviews of the studies conducted for exclusivity and also providing the drug, the latest drug product label and when available and necessary, we would also provide you the published literature pertaining to particular safety issues that may have arisen during these reviews.

We wanted you, of course, to consider in your review the limited ability to make causal inferences from spontaneous adverse event reports such as the ones we're going to discuss today. It's important to consider and weigh the known benefits of drugs against the known risks in making any recommendation about the significance of any particular adverse events that are discussed. We also need to weigh, consider the anticipated benefits of any regulatory action that we may take based on these reports against some unanticipated event, adverse effects that such an action may have.

So in all the evaluations, I think it's important to consider that there are benefits and there are also risks in doing one way or the other and all of those factors need to be weighed and that's not new to you. But I just felt that this would be important to put into the discussion here. As Diane has mentioned before, that we're going to present to you several products today and also tomorrow concentrating on methylphenidate. This is one of the drugs that has received exclusivity and is up for discussion. We have -- the FDA has identified a safety concern here and therefore, we will bring an extensive discussion and presentation on

methylphenidate tomorrow and that will be a new labeling action that we will be discussing pertaining to this product.

Coming to today's presentation, we have several products that will have what Diane discussed standard presentations. Now remember that we had mentioned that we'll have abbreviated versus standard and then extensive presentations, now, based on what the safety issue or the adverse events are indicating. For the first drug we have Ethinyl estradiol and norgestimate which is also Ortho Tri-Cyclen. The issue that will be discussed here is not particularly a safety issue in the sense that we've discovered an adverse event from the AERS reports but it's what will be very important to show the committee in terms of what an addition of negative information in labeling based on studies submitted for this particular product in pediatrics.

And the second drug is Detrol, Tolterodine. There is also an issue here that -- a new labeling action that the FDA has taken and that will be discussed in terms of the genesis and the background and the rationale for doing that. And then the third drug that will be discussed will the Ciprofloxacin. The adverse event review has

identified some serious adverse events which are known. They are labeled but a majority of exposures for unapproved indications and the context in which these adverse events are occurring is the main reason why we brought it to the committee.

Now, and the last part of the day, we're going to present four drugs in quick succession. And they have not -- the adverse event review has not identified any new safety signal from the one you review. And therefore, we will give you our abbreviated summary. We will provide you information on -- a brief summary on what the drug is, what the use pattern may be and if there are any descriptions of any adverse events and why we think that the one-year review has not shown or indicated a possible safety issue.

And I will end there and unless there are questions, I'd like to introduce the next presenter.

DR. NELSON: Dr. Glode?

DR. GLODE: I just had two very quick questions. One could probably be answered by our industry representative. If a consumer reports to the manufacturer a potential adverse event after a drug, does the primary source document get transferred or is there some interpretation that goes on or do they just

fax them a MedWatch form? What happens if you report that, you know, your 15-year old had a heart attack a week after starting Drug X and you write a letter to the manufacturer?

DR. GAROFALO: I can tell you that what we do -- I mean, there is an intake person and there's an exchange back and forth to try and get as much information as possible but sometimes we get very little -- you know, we get very little information from whomever calls but there's an attempt and a cycle to try and follow up and get as much information as we can to complete the form.

DR. GLODE: To complete the regular MedWatch form.

DR. GAROFALO: Yes.

DR. GLODE: Yes, I see. And then that comes to my second question; does the FDA have the authority and the ability to medically investigate a report? Sometimes it seems like there's very limited information as though maybe -- I'm thinking of very serious, potentially serious adverse events where there's maybe a call to the physician but there's not much there. Do you have the authority to go review the medical charts of people who died from Drug X if you choose to, if you start getting 10 reports from

Drug X?

DR. IYASU: Well, I'll refer that to the ODS folks, Office of Drug Safety but we do have the opportunity to follow up in every case and if the information is provided on the report form about who the reporter is. If it's anonymous, it will be very difficult to follow up on where. So we do have the opportunity. We do often call the originator of those reports. If there's additional --

DR. GLODE: Can you go beyond the physician. Can you go review the medical chart or is it a HIPAA violation or --

DR. IYASU: I'll ask --

DR. MURPHY: Do you want to answer that? Basically, we -- I say "we", ODS will call if they can get -- if we're looking at something serious, like you're saying, and they have the identifier, they will call, they will try to get as much information as possible. I don't want to make any statements as to what they would do as far as going to the Office. I can tell you that I know in the past that in certain situations, you know, any records that they could get their hands on they have done that, but I don't -- I'll ask you guys to address that.

DR. GIERHART: Brenda Gierhart, Medical

Officer DMEDP, HFD 510. The problem you cite is in the case of a death because you're unable to get the patient permission to obtain hospital records since most deaths would be associated with hospitalization and autopsy report. So then attempts can be made to try and find the family and get consent. In such a case, it's considered extremely important. I have asked for an FDA officer to present with a badge to the medical records department of a hospital and therefore, they are allowed to review the records and then they abstract from the records what is important and return that information to the reviewing division with the concern.

DR. GLODE: Thank you.

DR. NELSON: Victor?

DR. SANTANA: Can you clarify something for me? On your next to your last slide, under Cipro you have a bullet that says, "The majority of exposures for unapproved indications." Well, that's probably true for every medication that we prescribe in the United States, not necessarily their use or the approved indication, it goes beyond that. So how do you then -- what process do you go through when you have a scenario, this is a hypothetical scenario, where you're getting a lot of adverse events from your

review you determine it's because the drug is being used for an unapproved indication and then check that against the potential adverse events that may be occurring when the drug is used in the prescribed indication? Is there a process for you to gauge whether it's an issue related to the disease process or et cetera, et cetera? Can you kind of hypothetically answer that for me?

DR. IYASU: Well, it depends on the quantity and the quality of the reports that you get. If you have enough information to make some determinations as to whether there are significant differences in terms of symptoms or signs reported for each type of user. You're talking about different settings, different diseases. The postmarketing reports are not going to help you that much in that aspect but we -- if it's identified that there are unapproved or this is off-label, and there are a number of reports that are pertaining, you know, either increased frequency or increased severity with populations for which the drug is now approved for, then that's a cause for concern and that's why we're bringing it to the -- you know, we'll take it to further, I guess investigation.

We also try to see whether there's

literature pertaining to that. We've not specifically addressed that here in this presentation because we're focused on the one-year review, was there anything that we could present that would signify a potential safety issue that needed an immediate action, but this is a good question. The process is very cumbersome in terms of trying to disentangle underlying versus drug effect and that's very well-known to you from a number of discussions we've had.

DR. NELSON: Thank you. Do you want to introduce our next speaker?

DR. IYASU: Yes. Thank you. Our next presenter is Dr. Jean Temeck. She's a Board certified pediatrician and pediatric endocrinologist. She's been a member of the Division of Pediatrics Drug Development for two years. She's an acting medical team leader within that Division and the Division representative is Dr. Brenda Gierhart who will be sitting at the table for the duration of this presentation. She's a Medical Officer in the Division of Reproductive and Urological Drug Products.

DR. TEMECK: Good afternoon, Dr. Nelson and other members of the Advisory Committee. Thank you for coming today. Today I'm going to be speaking about norgestimate and Ethinyl estradiol. Background

information is that Ortho Tri-Cyclen and the lower estrogen dose product Ortho Tri-Cyclen low are oral contraseptive agents containing the progestional agent norgestimate and the estrogenic agent Ethinyl estradiol. In addition to contraception, Ortho Tri-Cyclen has been approved for the treatment of moderate acne vulgaris in females greater than or equal to 15 years of age who are unresponsive to topical anti-acne medications, have achieved menarche and who desire contraception.

These products are marketed by Ortho-McNeill. Ortho Tri-Cyclen was originally approved in July 1992 and Ortho Tri-Cyclen Low in August 2002. Pediatric exclusivity was granted in December 2003 based on conduct of a study to determine if Ortho Tri-Cyclen improves bone mineral density in adolescents with anorexia nervosa. Dispensed prescriptions for oral contraceptives increased from 92 million in 2002 to 99 million in 2004. Dispensed prescriptions for Ortho Tri-Cyclen brand and generic products decreased by 47 percent during the first year of post-exclusivity compared to the prior year. Ortho Tri-Cyclen was the third most commonly dispensed oral contraceptive product in 2004 down from number 1 in 2002.

Adolescent patients account annually for no more than approximately four percent of Ortho Tri-Cyclen prescriptions and no more than 6.6 percent of Ortho Tri-Cyclen Low prescriptions. Paralleling trends in adults the total number of pediatric prescription claims for Ortho Tri-Cyclen declined almost 76 percent from January 2002 to December 2004 while the total number of pediatric prescription claims for Ortho Tri-Cyclen Low increased over 100-fold during the same time period. These changes were expected since generics for Ortho Tri-Cyclen began to get approved in December of 2003 while brand Ortho Tri-Cyclen Low was first approved in August 2002.

Gynecologists, family practitioners and internists are the most frequent prescribers for these oral contraceptives while pediatricians write no more than five percent of these prescriptions. In females 17 years of age and older these products are most commonly prescribed during general counseling advice for gynecological examination. In adolescent females less than or equal to 16 years of age these products were also prescribed for the treatment of acne.

Now we will look briefly at the results of the study performed for exclusivity and update the findings originally posted on the website. This was a

one-year efficacy and safety study that was performed in response to a written request to assess the effective treatment with Ortho Tri-Cyclen compared to placebo on bone mineral density in female adolescents with anorexia nervosa. Exclusivity was granted based on a six-month efficacy end point. Specifically, this was Phase 2 double-blind randomized placebo controlled one-year clinical trial comparing Ortho Tri-Cyclen to placebo for the change from baseline in lumbar spine bone marrow density. A hundred and twenty-three adolescents, age 10 to 17 years who met the sponsor-modified DSM for diagnostic criteria for anorexia nervosa were enrolled. All patients were to be on a calcium and vitamin D supplement. The primary efficacy end point was the mean change in lumbar spine bone marrow density from baseline to cycle 6. Secondary efficacy end points included the mean change in lumbar spine, bone mineral density from baseline to cycle 13, the mean change in hip bone mineral density and body weight from baseline to cycle 6 and from baseline to cycle 13 and the mean percent changes in lumbar spine bone mineral density -- hip bone mineral density and body weight from baseline to cycle 6 and from baseline to cycle 13.

At the time of the interim report, 110

patients had a DXA scan at baseline and after six months of treatment. The primary efficacy analysis demonstrated a marginally statistically significant difference with a P value of .04 between Ortho Tri-Cyclen and placebo for the mean change in lumbar spine bone mineral density from baseline to cycle 6. However, the observed treatment difference of .01 grams per centimeter squared was notably smaller than the expected treatment difference of .05 grams per centimeter squared which the study was powered to detect.

Of the second efficacy end points only the mean percent change in lumbar spine bone mineral density from baseline to cycle 6 was statistically significantly different between the two treatment groups. However, again, the observed difference of 1.47 percent was noticeably smaller than the expected difference of six percent. As required by BPCA, these results were posted on the web. No change in labeling was made at this time. At the time of the final study report, 112 patients had a DXA scan at baseline and at the end of the study. There was no statistically significant difference between Ortho Tri-Cyclen and placebo for any of the efficacy end points at cycle 13.

During the trial there were no deaths and no thromboembolic events. However at least one serious adverse event was reported in approximately 13 percent of patients on Ortho Tri-Cyclen compared to approximately 23 percent of patients on placebo. In general the incidence of serious adverse events was similar between the two treatment groups with the exception of hospitalization for worsening anorexia nervosa which occurred more frequently in the placebo group and was the most common serious adverse event reported. Also in general, the incidence of any given adverse event regardless of severity, was similar between the two treatment groups with the exception of dysmenorrhea which was reported in approximately 16 percent of patients on Ortho Tri-Cyclen compared to approximately five percent of patients on placebo.

Labeling will be changed to incorporate the findings of this study to indicate that Ortho Tri-Cyclen is not effective for increasing lumbar spine and total hip bone mineral density in adolescents with anorexia nervosa. The labeling you see on this slide has been approved by FDA and I'll keep it up here for a few seconds so that you can have a chance to specifically read it.

Next I will be highlighting key

information from the package inserts for these products particularly as they relate to pediatrics and to safety. Like other oral contraceptive agents, contra-indications include patients with known thromboembolic or cardiovascular or cerebral vascular disease or risk factors for these diseases. Additional contra-indications include known or suspected pregnancy, breast or endometrial cancer, hepatic tumors and cholestatic jaundice. A box warning details the increased risk of serious cardiovascular adverse events in patients who smoke. These products are Pregnancy Category X. These products contain, in their labels, multiple serious adverse events in the Adverse Reaction section. The serious cardiovascular events include myocardial infarction, thromboembolism, thrombophlebitis and hypertension.

Serious cerebral vascular events include thrombosis and hemorrhage. Retinal thrombosis with resultant visual changes, including visual field cuts is also mentioned in the package insert. Since market approval, a total of approximately 1,000 spontaneous adverse events have been reported for all ages. Approximately 40 percent of the total have been serious, including 14 deaths. Approximately four

percent of these total postmarketing reports were in pediatric patients. Approximately, two-thirds of these pediatric reports were serious but there were no deaths.

During the one-year post exclusivity period, a total of slightly over 400 spontaneous adverse events were reported for all ages. Approximately one-third of them were serious, including three deaths. Approximately three and a half percent of the total were reported in pediatric patients. The majority of pediatric reports were serious although there were not deaths. Of the 14 unduplicated spontaneous adverse events reported in pediatric patients during the one-year post-exclusivity period, two were in utero exposures and 12 were adolescent exposures. Adverse events reported more than once were headache, metarasia, convulsion and drug exposure during pregnancy, the latter two unlabeled. Four patients were hospitalized, two neonates and two adolescents.

I will now detail the serious adverse events reported in pediatric patients during the one-year post-exclusivity period in the next few slides. Three serious adverse events included concomitant administration with isotretinoin and in two of these

three cases also with prednisone. All of these serious adverse events were acute on onset and they included benign increased intracranial pressure, depression and cerebral thrombosis. Since Isotretinoin and prednisone are labeled for increased intracranial pressure and depression, the first two cases are confounded. With regard to the third case, Ortho Tri-Cyclen is labeled for cerebral thrombosis. In all cases the events resolved upon discontinuation of Ortho Tri-Cyclen, isotretinoin and prednisone and with appropriate medical intervention.

Serious acute visual events occurred in three patients, all with concomitant therapy. The events resolved or improved with the discontinuation of Ortho Tri-Cyclen. The Office of Drug Safety performed an in-depth review of all cases of visual adverse events since product approval and they did not find a pattern. The current label for oral contraceptives warns of retinal thrombosis and states that these products should be discontinued if there is unexplained partial or complete loss of vision, proptosis, diplopia, papplledema, or retinal vascular lesions.

As mentioned previously there were two cases of in utero exposure. Both fetuses were exposed

to Ortho Tri-Cyclen Low during the first few weeks post-conception. One neonate was born breech at 34 weeks gestation and required two feedings but was otherwise healthy. The other neonate had seizures at approximately 24 hours of life that was found to be secondary to a right cerebral artery infarction which was diagnosed on both CT and MRI scans. The infant was discharged from the hospital on day six of life on anti-convulsive therapy.

Seizures occurred in two patients, on in the neonate that I just described and one in an adolescent with a history of seizures who was not taking anti-convulsive therapy. Since seizure was a comorbid pre-existing condition in these cases, there does not appear to be a safety signal. The remaining two serious adverse events were consumer reports. One of these was an isolated episode of acute hypertension, blood pressure 160 over 110, that was reported in an adolescent with a history of migraine who was taking Ortho Tri-Cyclen for approximately three months but no other medications. Hypertension is a labelled adverse event for oral contraceptives.

The other report consisted of three episodes of numbness of the right arm and slurred speech that occurred in an adolescent who was taking

Ortho Tri-Cyclen Low for an unspecified period but no other medications. Additional pertinent information in this case was not provided.

In conclusion, the number of pediatric adverse events roughly parallels the use. Although events were serious no pattern of new safety concerns was identified that is not addressed by current labeling for all contraceptive agents. Final assessment of the study conducted for pediatric exclusivity prompted new labeling. FDA recommends return to routine safety monitoring if the Advisory Committee concurs. I would now like to acknowledge the following individuals; from the Office of Drug Safety, Mark Avignon, Gerald Dal Pen, Andrea Feight, Adrienne Rothstein, and Kendra Worthy; from the Division of Metabolic and Endocrine Drug Products, Brenda Gierhart, Eric Coleman, Theresa Kehoe, Patricia Madara and David Orloff. Thank you.

(Applause)

DR. NELSON: Thank you. Open up then for any questions and to find out if we concur. Any questions or comments?

DR. DIAZ: In the last one with hypertension, what happened? Was the medication discontinued and what happened to the hypertension?

DR. TEMECK: It was a consumer report. The information was extremely scanty, so all we know is that this was an adolescent who was taking Ortho Tri-Cyclen for about three months. The patient had a history of migraine, was not taking any concomitant medications. We have really no additional information but hypertension is a labeled adverse event for OCs.

DR. NELSON: Judith?

DR. O'FALLON: I'm more comfortable with this than for some of the ones that we're going to see later today because it looks to me -- you've given us an estimate of the amount -- the number of prescriptions that have been processed during this year and the fact that we have 11 SAEs, serious ones.

Dr. TEMECK: Well, actually, there were 10 because one of those was a duplicate.

DR. O'FALLON; So the point here is that there's a -- compared to the rest of them coming down the line, there's a lot more information here and I feel more comfortable with going ahead and saying you've got a good -- you know, you've given us some good information.

DR. TEMECK: Thank you.

DR. NELSON: I guess we've got some things to look forward to, then, too, huh? Well then how

about just to do a quick show of hands of those who concur with the recommendation that's been made to us? Any abstentions or objections? So rather than read the names, I'll just say that all hands of all voting members were in the air.

I might just point out, I remember a couple of years ago, we were having a long debate about whether putting negative studies in the label was fostering off-label use. It seems we've now crossed that threshold which I would think is a wonderful threshold to have crossed.

DR. MURPHY: And I think that the comment that Solomon made earlier is really relevant. I think that the advocacy of this committee was important also in saying that we thought that the inclusion of negative information was important. I think we now track that for all of our products and clearly I think it is relevant to the physician that this product has been studied and I think the more we do this, the more they will understand that some of these that a negative study does not always condemn a product to meaning that it doesn't work. It just means the data we have at this point says it doesn't work the way it was studied. And I think that's an important educational program that we all need to continue to

provide, too. Thank you.

DR. TEMECK: Thank you very much.

DR. NELSON: Jean, are you going to introduce our next speaker or shall I?

DR. TEMECK: Yes, I will.

DR. NELSON: Go ahead.

DR. TEMECK: Dr. Larry Grylack is trained in pediatrics and neonatal/perinatal medicine. He practiced neonatal medicine for many years, primarily at Columbia Hospital for Women in Washington, D.C. He has clinical specialty interests in high risk infant developmental assessment and infant apnea. He has participated in clinical research and teaching. Dr. Grylack has been with the FDA for two years. And thank you very much.

DR. IYASU: Skip, I would like to introduce the Division representative, Dr. Lisa Soule, who is a medical officer in the Division of Neurologic Products for the city at the table and the presentation.

DR. GRYLACK: Thank you. Good afternoon. It's nice to see everybody again. I will be discussing Tolterodine today. Two drugs, namely Detrol and Detrol LA have Tolterodine as their active ingredient. Tolterodine acts as a muscarinic receptor antagonist. Detrol and Detrol LA are indicated for

the treatment of overactive bladder with symptoms of urge, urinary incontinence, urgency and frequency. The drugs are sponsored by Pfizer and received market approval at different times. However, pediatric exclusivity was granted at the same time for both drugs.

In terms of drug use trends in children, almost all use for both Detrol and Detrol LA were in the outpatient setting. Estimated pediatric prescriptions for the calendar year 2004 are listed on the slide showing that three and a half to four times as many Detrol LA prescriptions were written compared to Detrol. However, during the time frame of February 2004, to January 2005 the percentage of prescriptions for all ages that were given to children was higher for Detrol than for Detrol LA. An approximate 50 percent increase in Detrol LA use and an approximate 33 decrease in Detrol use were documented over the period between the time frame of February 2002 to January 2003 compared with the time frame of February 2004 to January 2005. So during that time span there was the increase in Detrol LA and a decrease in Detrol use.

Detrol LA prescription claims were approximately four times greater than Detrol claims

during the post-exclusivity period of February 2004 to January 2005. Looking at in-patient usage, discharges associated with mention of a Tolterodine product occurred in less than or equal to 0.2 percent of all hospital discharges during the year covering July 2003 to June 2004. On this slide I've listed the studies that were requested of the sponsor in the written request for the purpose of gaining pediatric exclusivity. Additional studies were submitted by the sponsor as well. Let's focus now on the studies done in neurologically impaired children.

There three 12-week open label, dose escalation pharmacokinetics, pharmacodynamic and safety studies. The age groups are different for the studies and the numbers are all relatively small. The doses for the escalation studies are listed on the slide. The milligram per kilogram per day dose and the formulation were the same in the one-month to four-year old study and the five to 10-year old study. The concentration used for those studies was one milligram per 5 cc's of syrup. In the 11 to 15-year olds the doses listed are total amounts, that is milligram per day and the formulation was a capsule unless the patient was unable to swallow the capsule in which case the capsule was opened and the beads

sprinkled on their food.

Of all the patients enrolled in these three studies, 78 percent had a myelomeningocele with the others having a spinal cord injury or anomaly. The results showed that urodynamic data were inconsistent both within and across the three trials. Secondly, there was a lack of dose response trends across the studies. The safety data from these trials will be addressed subsequently in my presentation.

Next, I will review the studies done in so-called neurologically intact children for the treatment of over-active bladder with symptoms of urge, urinary incontinence, urgency and frequency. Two randomized, double blind placebo controlled trials were conducted over a 12-week period using a dose of two milligrams per day of Detrol LA. The trials were both conducted in five to 10-year olds and the number of patients are listed on the slide. The primary efficacy end point for both studies was changed from baseline in the number of weekly incontinence episodes during waking hours. The results showed no statistically significant differences in outcomes comparing Detrol LA to placebo.

In turn, the label for Detrol LA states that efficacy in the pediatric population has not been

demonstrated. Turning our attention to safety, we will focus on the data from pediatric studies, including those done for exclusivity and other studies conducted by the sponsor. The data base was composed of 917 unique patients who were exposed to Tolterodine. The reason I use the word "unique" is that some of these patients were also enrolled in longer term open-label safety extension studies. There were no deaths recorded but there were 24 serious adverse events in 20 patients. Among the SAEs were lower urinary tract infections and four pyelonephritis, one of which was actually in the placebo group so not among the 917 Tolterodine exposed patients. Of the non-serious adverse events, the -- that occurred in the study populations, 18 patients demonstrated aggressive and/or abnormal behavior.

Based on the safety studies from the pediatric studies, the Detrol LA label was changed to include information about an excess of urinary tract infections and abnormal behavior in Tolterodine treated patients compared to placebo treated patients. At this point, I would like to summarize the labeling changes that resulted from the pediatric exclusivity trials. Based on the studies done with Detrol LA, its label was changed to incorporate the information

listed on this slide. The label states that efficacy was not demonstrated, as we mentioned earlier. From a pharmacokinetics standpoint, the labeling reflects the facts that the dose-plasma concentration relationship is linear and that the ratio of the parent compound to metabolite differ depending on what type of metabolizer the patient is.

Third, labeling indicates that the percentage of urinary tract infections in five to 0-year olds was higher in the drug treated group compared to placebo. Finally, labeling indicates that aggressive, abnormal and hyperactive behavior disorders were higher in patients treated with Detrol LA compared to placebo. There have been no changes yet in the pediatric section of the Detrol label to date. However, the FDA's Division of Reproductive and Urological Drug Products has requested that the sponsor submit a revised Detrol label and we are told that, in fact, the sponsor has responded in an affirmative fashion to the Division.

This next slide is definitely not busy. Based on the adverse events reporting system, the FDA's Office of Drug Safety reported that there were no adverse event reports associated with Detrol or Detrol LA usage during the one-year post-exclusivity

period. In addition, the Office of Drug Safety conducted a search and analysis of pediatric adverse events during the postmarketing periods for both Detrol and Detrol LA. Keep in mind that the postmarketing period for Detrol is longer than for Detrol LA. A combined number of adverse event reports for both drugs was 31 with 29 of them being unduplicated. Twenty-five of the reports were associated with Detrol and four with Detrol LA. Where data was available, there was a positive de-challenge in 15 patients, in other words, as Dr. Iyasu had pointed out sometimes disappeared when the drug was discontinued, and there was a positive re-challenge in other words, symptoms reappearing when the drug was restarted in one patient.

Of the 29 patients with adverse events associated with these drugs, anti-cholinergic events were cited in nine reports. The symptoms are described on the slide. Events representative of central nervous stimulation were cited in eight reports with the symptoms described in the slide as well. Anticholinergic and central nervous system simulation together were cited in two reports; Urinary tract infection in two, medication error in three and other categories in five and some of these

others will be described subsequently under the serious adverse events.

I have indicated by notation which findings are unlabeled. With the asterisk I have indicated aggression and hyperactivity as being unlabeled in the Detrol label but, again, as I mentioned earlier, that will change since the sponsor has responded affirmatively to the Division's recommendation for change in the Detrol label. With underlining, I have indicated a confusion, overheating and flushing are unlabeled in both the Detrol and Detrol LA labels.

Let's look at the 18 reports that were graded as serious. "Review of these events in collaboration with the Office of Drug Safety showed that there were no deaths, five hospitalizations, one disability, two patients who were older than 16 years of age and -- they tried to sneak in, in the pediatric adverse incident -- and 10 events considered to be non-serious. Therefore, we are left with six serious adverse events. This slide details the six serious adverse events, including the five hospitalizations and the one disability. The hospitalization I have listed first was the only event where the symptoms were thought to be possibly related to Tolterodine.

Symptoms in this patient were breathing difficulty, nocturnal laryngitis and cough which resolved after Tolterodine was discontinued, so one of the positive de-challenges.

The symptoms in the other patients who were hospitalized are also listed on this slide. The one disability reported was described as hyperactivity but there was not a lot of additional detail in that report. As I alluded to earlier, the Division of Reproductive and Neurologic Drug Products has requested from the sponsor that safety information currently existing in the Detrol LA label be incorporated into the Detrol label specifically information about the increased incidents of urinary tract infections and abnormal behavior in Tolterodine treated patients compared to placebo.

The sponsor has also been asked to include information about the lack of pediatric efficacy in the Detrol label. And as I mentioned, Division has reported that the sponsor has responded in an affirmative manner. In closing I am affirming that the one-year post-exclusivity monitoring period for Detrol and Detrol LA as mandated by the BPCA has been completed. Secondly, the FDA recommends that these drugs return to the FDA's routine monitoring after a

change is made in the Detrol label. I ask whether the Pediatric Advisory Committee agrees. And I would like to acknowledge the individuals from the Office of Drug Safety and the Division of Reproductive and Urological Drug Products listed on this slide for their work in support of this presentation. Thank you for your attention.

DR. NELSON: Thank you. Questions? Mary.

DR. GLODE: On page 45 for the committee on the slide of the summary of the labeling changes resulting from the exclusivity studies, I don't know exactly what the labeling change will say but -- right there -- it would certainly be helpful to me as a physician, if I was reading the label to have some statistical significance here so either say in -- you know, in a study involving 917 patients, or whatever that the postmarketing study showed, or to have P value there or numerator and denominator, so I know whether the percentage of UTIs was statistically significantly higher and had some grasp of whether that was a clinical significant difference.

DR. GRYLACK: The label for Detrol LA reads that a total of 710 pediatric patients, 486 on Detrol LA and 224 on the placebo age five to 10 with urinary frequency and urgent incontinence were studied in two

phase three randomized so forth studies and then gives the percentages with UTIs and --

DR. GLODE: Does it give a P value then?

DR. GRYLACK: It does not in the label.

DR. GLODE: Okay, I would recommend that it include that.

DR. NELSON: Bob?

DR. WARD: I have the same question but it had to do with the background book. The frequency was 6.6 percent in treated patient and 4.5 percent in placebo and without knowing the power, that difference didn't sound particularly different.

DR. GRYLACK: Dr. Soule, as was mentioned, is from the Division of Pediatric --

DR. SOULE: Yeah, one of the difficulties with safety reporting from these clinical trials is that typically there are no safety hypothesis specified and they're not subject to formal hypothesis testing, nor powered for those end points, so what we tried to do in the label was simply provide a description of what was observed.

DR. WARD: But we hold our efficacy to the standard of being statistically significant. And I think we should do the same thing for the adverse events. So if the 6.6 percent is not different

statistically, than the 4.5 percent then I don't think we can have them put that in the labeling. I mean, it's a double standard it appears to me.

DR. SOULE: Well, again, it was simply trying to describe what we saw in the studies.

DR. GRYLACK: It depends whether the studies are powered for safety to begin with and --

DR. WARD: Right, no, I understand that, but do you see my point, if --

DR. MURPHY: I think, Bob, though one of the issues though, is that the agency always feels that it errs on the side of providing the data versus not providing the data, particularly when you have not designed -- you don't know what the adverse event -- I mean, sometimes you do, but when you don't know what the adverse events are going to be, and you end up with X number and they're higher, it's just like our adverse event reporting postmarketing in a way in that we don't -- we don't require that that be statistically -- because you can't -- now, in a study you could, I understand what you're saying but that assumes that you set out to test the hypothesis, and I think that since you don't know always what those events are going to be, I think what the Division has tried to do is to look at the events, decide whether

they think they are different or not within the limitations of having not defined up front what the test was going to be.

And if it's -- and if it meets some of those other criteria, it makes sense, you know, you mobilized your bladder, you may get higher -- you know, then they feel, I think, that it would be better to err on the side of providing that information with its limitations. So I guess that's my concern, to say we can't report anything if it doesn't have a P value. I mean, that would be very problematic.

DR. WARD: But then wouldn't you feel that you had an obligation to put the data in as the data are, that is in the treated group, the frequency of UTI was 6.6 percent and with a sample size of what, 700 or something patients, and was 4.5 percent in the placebo treated group, so that the physician could then make a decision based on numbers, not a qualitative statement. Do I think this risk is worth it in this particular patient that has a hyperactive bladder.

DR. NELSON: I guess I hear two different things being said. Many labels include tables that list adverse events relative to the groups without P values because they're not powered to answer that as a

first point. The second point is, if by chance you found one that was statistically significantly different but you thought the risk benefit was still in favor of approval, putting a P value in the label if it is in fact statistically significant might be of help to those of us who don't have our calculators with us as we're reading the label. So there's really two different issues there, Bob.

DR. WARD: I think we need the raw numbers to make an assessment but I think that it is worth putting in -- I think we should put in the P value about the adverse events, even though it wasn't powered to detect a difference and it was powered to detect a difference in efficacy but not a difference in adverse events. I think the P value should be there but I think the raw numbers should be there as well.

DR. NELSON: I assume a P value only if it reaches less than .05. I mean, listing all of them .5, .4, .6, .2.

DR. WARD: If we feel that this is significant enough to put in the label, yet it's not statistically significant, I would like to see the p value put in there that indicates what the actual P value is.

DR. GRYLACK: You know, obviously the wording is what counts here, I mean, how you say it. When I read higher, that's an implication to me. Okay, there was no other way to say that, just to list the numbers, so I think it's what you imply and if you don't have the power to know whether they're different than maybe we should say, we don't know whether they're different.

DR. NELSON: So I guess the point there being use of the word higher may not imply a statistical test but is often read that way. And that a tabular format, if, in fact, it's not statistical, would be a more accurate representation of the data.

DR. WARD: You couldn't say that in the results section unless it was statistically significant.

DR. NELSON: Right, right. Judith.

DR. O'FALLON: The -- pertinent to this discussion, I think what might be helpful would be to use confidence intervals. They are descriptive. You know, that's what they are and they reflect both the number of events that you saw and the size of the number of the patients that were treated or the people that were treated. And physicians will quickly learn two things. One is that if the confidence intervals

do not overlap, you've got a significant and the second thing is, remember, if you're using a .05 level test, you expect to see one in 20 of them being false positives. So if you're looking at all kinds of adverse events, you're going to see some that are significant when they really aren't. So these are some of the issues that they're concerned about, but I would say that using a confidence interval estimator in the -- in a table would help physicians to get some idea of the -- you know, the size of the occurrence based on that sample, okay?

DR. NELSON: That's assuming a level of statistical significance understanding.

DR. O'FALLON: You will learn. We all will learn.

DR. NELSON: Let me go first to our statistician, our other statistician, I should say, Tom and then Bob.

DR. NEWMAN: I just agree emphatically with Judith that this is -- I mean, what the clinician wants to know is, is this difference anything bigger than what would be expected by chance based on the numbers in the study and who big a difference is consistent with the results of the study and the confidence intervals are much more informative than

just the numbers, also more informative than the power, so it's really -- I would strongly support that.

I just wondered whether this labeling -- there may be more to it than what I read here. I hope that the extent of the discussion of the randomized double blind study is not just efficacy not demonstrated but that similarly there's you know the point estimate of 95 percent confidence interval for the efficacy because this drug was studied in 500 children and apparently no efficacy was demonstrated and so I mean, just saying "efficacy not demonstrated" doesn't tell the doctor that the study was done with 500 kids and it didn't work. It just says for all they can tell, there was no study done. I mean, that was true before -- efficacy not demonstrated was true before the exclusivity study was done.

So point estimate 95 percent, confidence levels for efficacy -- and is my understanding of the PK data, there was no dose response, you know, a full difference in dose from .03 to .12 and there was no dose response and there was inconsistent results on the urodynamic studies? Is that all basically saying the same thing, that the drug doesn't work?

DR. SOULE: Would you like me to read the

actual language from the label?

DR. NEWMAN: Sure.

DR. SOULE: And this appears in the Pediatric Use Section, we have a statement, "Efficacy in the pediatric population has not been demonstrated". That's followed by the following paragraph. "Two pediatric phase 3 randomized placebo controlled double blind 12-week studies were conducted using Tolterodine extended release, Detrol LA tablets. A total of 710 pediatric patients (486 on Detrol LA and 224 on placebo) age 5 to 10 years with urinary frequency and urge urinary incontinence were studied. The percentage of patients with urinary tract infections was higher in patients treated with Detrol LA, 6.6 percent compared to patients who received placebo, 4.5 percent. Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9 percent of children treated with Detrol LA compared to 0.9 percent of children treated with placebo."

DR. NEWMAN: So, yeah, I guess what I would want is a point estimate 95 percent confidence interval for the efficacy and I think efficacy not demonstrated is kind of an under-statement because the study was powered to look for efficacy and it didn't

find it, so I think you could say lack of efficacy was demonstrated.

DR. NELSON: I guess two comments. I agree with Tom and there's a marked difference between -- I mean, what you read sounds similar to the Ortho product which is good but it wasn't -- I mean, you're reading from a document that I guess wasn't in the briefing book, nor on the website which I downloaded this morning. So it was unavailable. Where is it? I mean, I just -- 185, interesting, there's two Pediatric Use sections. There's two labeled, one for Detrol LA and one for -- All right, so I was looking under the wrong label. So will it be in both?

DR. SOULE: Yeah, it's currently in the LA label and as Dr. Grylack reported, they have agreed to add this to the Detrol label also.

DR. NELSON: That is the source of confusion, thank you for clearing that up. Richard.

DR. GORMAN: Could the FDA develop a standard shorthand for those of us who don't read the label in as much depth as our eminent statisticians and clinical epidemiologists and just sort of -- where it says "Pediatric Use" say "after adequate controlled trials efficacy was not demonstrated," and then put all that detail behind it, something that starts out

with "it has been studied, it doesn't work in this population."

DR. MURPHY: This gets back to the original issue, okay? If you look back to certain classes of products two negative studies don't mean that a product doesn't work. And so that's our quandary. And it's trying to word it that this is what we have, folks, that's it. And again, I think the confidence interval is something that we at FDA understand how useful that can be but we've made a quantum leap to put in negative data. If we start trying to make a book out of it, we're -- you know, we just -- but we want it to be informative, so we take -- we will take this back and there may be a way that we can -- you know, if we're going to say randomized double blind, blah, blah, blah, you know, maybe we can get some other information in there, too. I just want to balance, you know, trying to make it informative with the limitations of knowing that often in some classes of products you may have three or four more studies then there might be positive.

DR. NELSON: Judith?

DR. O'FALLON: Every study has to tell what its power -- you know or every good study anyway, has to say how much power it has to detect what words of

clinically significant differences that are looking -- they're looking for. It may very well be that you could have a statement saying "studies with 80 percent power to detect differences of this sort failed to find a difference," you know, and that would be a sentence, but it would give people a feeling for how negative these studies really were.

DR. NELSON: Dennis?

DR. BIER: You know, earlier this afternoon we were talking about the surfactant thing. If somebody here at the table had said, "We can't provide this information on the informed consent to the parents because they wouldn't be able to understand it, and we shouldn't inform them," we would have all stood up and you know, yelled and screamed. So I think we should apply the same standard to the people who are going to prescribe the medication.

DR. NELSON: Victor.

DR. SANTANA: Having sat on this committee for awhile, I think I've very sensitive to this issue that our task is not to rewrite the label for the FDA. So let's be careful here in terms of what we're saying. That's not our duty. Our duty is to advise the FDA on what we think are important points that they may want to consider when they review this label.

And to me the important points is that in the efficacy section, you do have to state the number of studies that have been done. The efficacy study should have been powered to detect a difference, so you must give a P value in the efficacy section.

Now, you give all the other numbers that you want. I think in the side effect adverse event, I kind of disagree a little bit with the biostatisticians. The studies are not powered to detect differences in terms of toxicity than it's redoing statistics after when the study's done and one has to be very careful but in that section, one could provide the raw data which, I think is what the committee is saying, "Tell us what six percent is; is it two out of X number or is it, you know, 500 out of 10,000." Give some number that then the clinician can personally weigh what the value of that is.

I'm not in favor of doing retrograde statistics for toxicity if the studies were not designed to detect those differences.

DR. WARD: But do you think it's fair to say it is higher?

DR. SANTANA: No, I disagree with that word, yes. I do disagree with that word. I think that implies a judgment that we should not be making.

DR. NELSON: So I'm beginning to detect a consensus of remarks and so I'm going to ask if we can provide feedback on the question whether we concur and allow me to clarify that. Concur is specifically with the labeling that we had read to us and not the language that was presented in more briefer fashion on the slide. And so I guess I'll ask with the additional advice that we've provided, whether we at least concur on this particular product with the labeling changes and then the routine monitoring going forward, two questions.

DR. WARD: Can you clarify which language you're talking about, Skip?

DR. NELSON: Well, let's just ask about the monitoring, which is the question they're asking us. They're information us about the label, I guess from that standpoint, so in terms of monitoring.

DR. GRYLACK: Yeah, the question, as I understand it is, can routine monitoring continue given that the change is going to be made in the Detrol label?

DR. NELSON: Right, going forward.

DR. MURPHY: In other words, we would not bring this back to you, okay, that's what we're saying.

DR. NELSON: Right.

DR. MURPHY: We would not bring back to the committee ongoing review of adverse events. We would -- it would go back through the usual process with the Division looking at it.

DR. NELSON: Go ahead, Judith.

DR. O'FALLON: This is my problem. It's a process one. I can't figure out -- it will -- those are wonderful reports that you put together. I want to thank you very much for all the information. There are enough unstandard ways of giving the information that makes it hard to get at it, but from what I can tell, is you had about 68,000 prescriptions or something for -- during this postmarketing year and no adverse events, serious adverse events. Now, I'm -- you go back and use the postmarketing, which is dependent upon the fact that there are two rather different follow-up periods for these two. Is this an adequate process to use to say it's okay, it looks like we don't have any new information, we can go back to just plain old regular monitoring, or should we be saying there's not enough information yet available to make that judgment?

DR. GRYLACK: Well, the reason that the -- you know, since there was a signal, especially with

paradoxical CNS stimulation events is that, you know, got the Office of Drug safety to go back and do the postmarketing study in addition to the post-exclusivity, so then if you're recommending additional monitoring, the question is how much longer are you going to -- you know, so I think that has to be considered as well.

DR. IYASU: Could I add something? I think we have to provide some context for this. We -- the review was for the one year. In fact, if you look at the postmarketing reports that came from FDA for pediatrics there were up to zero reports in 2003, 2004, 2005. This labeling action that has been discussed today is really to update the Detrol label because of information that we had from prior reporting pertaining mostly to this particular product. And from the corporate trials we have known that there are issues related to the CNS stimulation and at the time that this was approved, the label included the information about this possible safety issues. So the issue now in terms of re -- updating the label for Detrol is based really on those prior reports and also supplemented by the corporate trial data and we don't believe that there's a difference between -- there's no reason to make a distinction

between those two products, given that they can occur in both.

So when we ask you if you concur with the -- with taking Detrol into the monitoring -- into the routine monitoring, it's really basically that we haven't seen any safety issues in the last three years. We have this prior information and that is being addressed in the new label and is -- there have been questions about whether that is an adequate description that would be helpful to the prescribing community in order for them to assess, and I think that's a legitimate question.

I also want to say that the largest summary for the reviews for those critical trials is available on the web as you well know and it's also included in the -- in your packet, so that is something that many, many prescribing physicians may not -- are not aware of but that is something that we have to make sure that people are aware of. There is additional information that's available on the web.

DR. MURPHY: I guess, let me ask you, Judith, because what Sol is pointing out is the slides, again, we -- this would fall into our category of not having a safety issue, just wanting to inform the committee about the information because when you

look at the review, not the slides, you know, we do give you approval and there is, you know, a pretty consistent pattern that we're not seeing anything new. So I guess that's why we're saying we're not -- we're giving you -- if there is so little in the one year, we do go back and look at the prior after we've had lots of conversations about this, you know, because you have so little.

We do go back and look. And if we don't see anything there, then we -- that's where we say we don't think we need to do it more. So that was why it wasn't just the zero this time, it was looking back over the total history so far.

DR. O'FALLON: Well, for me it was just a question and it came up because I was looking at all of them, okay, as to how much is enough information, I mean, how many prescriptions say or people should be treated, pediatric people, should be treated before we can say, "Well, we didn't see much of anything so we're pretty confident that not much of anything was happening". If you treat 100 and you get nothing, that has a different meaning than treating 1,000 and having nothing. Do you see what I mean, and I'm just asking.

DR. MURPHY: I think in our prior

discussions that one of the things we didn't come up with was a set number. Okay, we're going to look at this until we had so many prescriptions. We didn't -- what we've been trying to do is, again -- and we're delighted to receive your feedback, is say, "Okay, right now our approach is we don't see anything. We're going to look at those previous years and if we still don't see anything, we're" -- if there's a low use, you'd have to go for a very long time to see anything. So our approach is that if we don't see anything we'll look back to the prior years. If we don't see anything there, then we're going to say we don't think there's anything there.

DR. NELSON: For the sake of clarity, I'm assuming by saying routine, it means it doesn't come back to this committee. It does not mean the Office of Drug Safety does not continue to investigate serious adverse events that are reported. So, you know, I think we need to keep that in context. It's not as if they stopped doing their job. They're just saying, they need to come back and report to us in a year as to what they've done in that year unless there's a specific question. Is that fair?

DR. O'FALLON: Does it mean you do continue to do the same level of monitoring or is it just

reporting? I got the impression it was a change in monitoring procedures.

DR. MURPHY: I think it would be unfair to say that having this meeting doesn't reprioritize things sometimes. I think we have to be quite honest about that but no, the monitoring, the reports go in and certainly as Dr. Nelson said, anything that comes in that's serious gets its usual rapid review and in-depth review. It's -- what they get are counts and they tend to look for patterns, okay. So unless there's something else that comes in like a serious -- or a peak, they won't possibly go into as much depth as we might getting ready for these meetings. But yes, the reviewing still goes on, just with a different group as far as not reporting back to us.

DR. GRYLACK: I just want to say that in terms of the drug use, you know, I think we are fortunate to be able to capture the Detrol adverse events because if you look at the usage, you know, the Detrol usage has been decreasing, so the fact that 25 of the 29 unduplicated reports were associated with Detrol speaks to the fact that you know, we, I mean, the Office of Drug Safety, was able to capture that and therefore, provides support to the change in the Detrol label to go along with the Detrol LA.

DR. NELSON: Thanks. In the interest of trying to keep our public hearing within its time framework, I'm going to ask if we could come to a conclusion about whether we concur or not, so I guess I'll ask all those who would concur with the recommendation for this to be routine monitoring from here on out in the context of the labeling changes that we've seen, raise your hand. And any abstentions or objections? I see none. Thank you.

Let me ask if there are individuals who would like to speak during the open public hearing. I see none, I hear none, so there must be none, I guess unless we don't have enough people in the audience to do a proper sampling, but --

(Laughter)

DR. NELSON: All right, Larry, do you want to introduce Alan?

DR. GRYLACK: Well, on the chance that they're already getting up to raise public issues, I stayed around so I could introduce Dr. Alan Shapiro, who is a pediatric infectious disease specialist with a PhD in biochemistry. His past research includes working immunology infectious diseases and molecular pharmacology. He has also had training in pediatric nephrology and medical genetics. Dr. Shapiro has been

with the Division of Pediatric Drug Development for almost two years working as a medical officer and has been a valued colleague of mine.

DR. NELSON: Solomon, your microphone.

DR. IYASU: I want to introduce Dr. Joette Meyer, who is a clinical reviewer with the Division of Special Pathogens and Transplant Products, who will be sitting and be a resource during this presentation.

DR. SHAPIRO: Thank you. Thank you, Larry. I'd like to go over the adverse events for Ciprofloxacin. Ciprofloxacin, also known as Cipro, is an anti-bacterial that gained original market approval in October of 1987 and has many adult indications and its pediatric indications include post-exposure inhalational anthrax and second line therapy for complicated urinary tract infections and pyelonephritis in patients one to 17 years of age. The sponsor was granted pediatric exclusivity in December of 2003.

I'd like to discuss the drug use transfer Ciprofloxacin, systemic Ciprofloxacin accounts for roughly 41 percent of the 33.5 million prescriptions dispensed for the quinolone class in the United States in 2004. Dispenses prescriptions for systemic Ciprofloxacin have increased slightly from

approximately 13.6 million in 2003 to 13.8 million in 2004. Pediatricians were responsible for approximately one percent of the prescriptions dispensed for Ciprofloxacin tablets in the US during 2004 and approximately 17 percent of the suspension formulation dispensed during the same time period. From the IMS National Disease and Therapeutic Index from 2002 to 2004, 13 to 26 percent of the total use in pediatrics was for the treatment of urinary tract infections. It was unclear what fraction of these infections were complicated UTIs and therefore, we can assume that most of the use of Ciprofloxacin was off label.

Now, I'd like to discuss the pediatric exclusivity trials. The first was a controlled safety trial with efficacy data being collected and the second was an open label safety trial. The first trial which was a controlled safety trial consisted of a perspective randomized double blind trial with patients with complicated urinary tract infections or pyelonephritis ages one to 17 years in which Ciprofloxacin was compared to intravenous ceftazidime, oral cefixime or oral trimethoprim/sulfamethoxazole. A subset of these patients participate in the pharmakinetic study which contributed to the labeling

pediatric dosing recommendations.

As part of this study, there was a muscularskeletal evaluation and there was an independent pediatric safety committee that performed a blinded review of all cases of muscularskeletal adverse events. These included patients with an abnormal gait or abnormal joint exam. Cases were evaluated for evidence of clinically diagnosed or possible evidence of arthropathy. Arthropathy was broadly defined as any condition effecting a joint or periarticular tissue that may have been temporary or been permanent. The muscularskeletal events evaluated by the safety committee are listed below. I should mention that the majority of the adverse events reported were arthralgia.

Now, going over the results of the controlled safety trial, I went to mention from our prior discussion there are confidence intervals in the label where you will see that 95 percent confidence interval for the safety trial. And in regard to arthropathy events, at the six-week follow-up, 9.3 percent of the Ciprofloxacin patients versus 6 percent of the comparator had arthropathy events. And at the one-year cumulative follow-up, 13.7 percent of the Ciprofloxacin patients versus 9.5 percent of the

comparator patients had arthropathy events.

I should mention that all these events did resolve by one year's time. Going over neurological adverse events, at six-weeks follow-up, three percent of the Ciprofloxacin patients versus 2 percent of the comparator had adverse events. And I should emphasize that towards the end of this slide is that the most frequent adverse event were gastrointestinal with 15 percent of the Ciprofloxacin patients versus 9 percent of the comparators who had adverse events.

Now, going over the controlled safety trial also collected at efficacy data and on this one we also have a 95 percent confident intervals that you can look up in the label. So we have a favorable clinical response in 96 percent of Ciprofloxacin patients, versus 93 percent of the comparators. Bacterial eradication was in 84 percent of the Ciprofloxacin patients, versus 78 percent of the comparator.

Now, going onto the second trial which was an open label safety trial. This was a perspective non-randomized open-label observational study that evaluated the long-term muscularskeletal and neurological system health in pediatric patients two months to 16 years who received Ciprofloxacin versus a

non-quinolone antibiotic. I should emphasize the enrollment, choice of antibiotic, dosing regiment and treatment duration were determined at the enrolling physician's discretion. And also that the same definition of arthropathy was used as in trial 1.

Now, with -- because this was a non-randomized observational study, we were not able to make direct comparisons between Ciprofloxacin versus the non-quinolone comparator. Therefore, I'm only going to mention the rates for Ciprofloxacin here. So at six weeks of follow-up, for any muscularskeletal events there was nine percent of total adverse events reported were muscularskeletal and the majority of these were arthropathy, which was eight percent of the total adverse events. Neurological adverse events were seven percent of the total reported.

Now, going to the one-year post-treatment follow-up, the total for muscularskeletal events were 13 percent of the total events reported, again, the majority being arthropathy at 11 percent of the total and neurologic was 11 percent of the total. Now, going on to labeling changes that derived from these exclusivity studies; Ciprofloxacin was approved as a second line treatment of complicated urinary tract infections and pyelonephritis in patients one to 17

years of age. It was not a drug of the first choice, due to increased incidents of adverse events compared to controls including events related to joints and surrounding tissues.

As we had discussed earlier, in the complicated UTI clinical trials, the -- Ciprofloxacin versus the controlled, there were -- there was a larger amount of gastrointestinal and arthropathy adverse events. And the label was also informed with pharmakinetic and dosing information for the intravenous and oral formulations.

Now, I'd like to go over the adverse report since marketing approval for Ciprofloxacin. There were over 10,000 reports of adverse events in all age ranges. Of these pediatric reports, there were 228 reports which -- of which 142 were serious and there were 13 pediatric deaths. Now going on to the time period post-exclusivity period for Ciprofloxacin for all age groups, there were over 600 reports of adverse events. In the pediatric age, there were 19 adverse event reports which consisted of 17 unduplicated reports, all were serious and there was one pediatric death. Now, on the next slide I'm going to give you an overview of the types of adverse reports we had.

As you can see here, we had 17 adverse event reports and you can see the breakdown here. I'm going -- in my subsequent slides, I'm going to be discussing the pediatric death, the muscularskeletal adverse events, central nervous system adverse events and the gastrointestinal adverse events. As Solomon eluded to about Ciprofloxacin, of these adverse events, 12 out of the 17 patients with reported adverse events were receiving Ciprofloxacin for an unapproved indication for pediatric use.

Now, going onto the post-exclusivity pediatric death, this is an adolescent female with chronic mucocutaneous candidiasis and common variable immunodeficiency admitted with a one week history of progressive dyspnea on exertion. This patient had a complicated hospital course, treated with multiple medications, was diagnosed with Candida tropicalis fungemia, developed mucosal and gastrointestinal bleed, liver and renal dysfunction. The patient died due to uncontrolled gastrointestinal bleeding. The possible ideologies for these bleedings include diffuse intravascular coagulation due to fungal sepsis, liver or renal dysfunction, and lastly, possibly hematological/coagulation dysfunction related to Ciprofloxacin.

Now, to discuss the musculoskeletal events that occurred in the post-exclusivity period; the first one is a 12-year old who experienced tendinitis, back, hip, knee and heel pain three weeks after taking Ciprofloxacin for a temporal osteomyelitis that followed facial surgery. This patient had a history of Crouzon's syndrome, acanthosis, a ventriculoperitoneal shunt and osteitis. She received a total of five weeks of Ciprofloxacin oral therapy for outpatient treatment of osteomyelitis. The MRI by report showed knee effusion and some thickening of the cartilage. The diagnosis was tendinitis of the tibia, patella and Achilles tendon. Patient could not stand or ambulate and required a wheelchair a month after the medication was discontinued. I should mention that we have obtained further report on this patient. This patient is still having difficulty ambulating and is still weak.

Now, on the second musculoskeletal adverse event, this is a patient that also has prolonged disability. It's a 10-year old treated for a post-operative abscess with persistent leg pain and inability to run. I should emphasize this is a foreign report. This patient started Ciprofloxacin therapy for post-operative abscess, developed knee

pain during treatment and Ciprofloxacin was stopped after four days of therapy. The patient was confined to bed during the entire hospitalization. Pain was persistent and considered disabling and patient was unable to run.

The next two adverse events -- musculoskeletal adverse events were patients where the musculoskeletal problems resolved following discontinuation of therapy. The first one was a 14-year old with osteomyelitis of the little finger treated with 14 days of Ciprofloxacin. The patient developed Achilles tendinitis after one week of therapy which increased in severity by 10 to 14 days. Ciprofloxacin was discontinued and patient improved. The second patient was a 15-year old with chronic osteomyelitis of the left radius and developed joint stiffness and ecchymoses in both knees while on Ciprofloxacin. Symptoms resolved within two weeks of discontinuing therapy.

Now to summarize the musculoskeletal events; the potential for severe adverse events in joints and tendons subsequent to the use of quinolones is addressed in several sections of the Ciprofloxacin label and the warning, precaution and adverse reaction sections. These adverse events include rupture of the

Achilles tendon, pain and inflammation of the tendons, joint stiffness, tendinitis, pain in extremities and effects on joints. Now moving on to the post-exclusivity central nervous system adverse events. This is an eight-year old patients who had seizures before and after Ciprofloxacin in therapy but this was in the setting of numerous concomitant medications and underlying brain cancer. The second patient was a 15-year old who developed status epilepticus while on Ciprofloxacin and cefepime therapy for the treatment of a urinary tract infection. Both drugs were discontinued and the patient recovered.

Convulsions are addressed in the warning section and also in the adverse reaction section of the labeling, where it states that during clinical trials convulsive seizures were reported in adults.

Now, moving on to our gastrointestinal post-exclusivity adverse event, this is an eight-year old with severe pseudomembranous colitis and ascites following therapy with co-trimoxazole, cefotaxime and Ciprofloxacin. The event resolved with corrective treatment and did not reoccur. In the warning section of Ciprofloxacin label, pseudomembranous colitis is discussed. I should also emphasize the pseudomembranous colitis has been reported with nearly

all antibacterial agents and may range in severity from mile to life-threatening.

Now, to conclude, on our review of the 17 unduplicated pediatric cases showed mostly labeled adverse events. Twelve out of the 17 patients who developed adverse events were receiving Ciprofloxacin for unapproved indications for pediatric use. This completes the one-year post-exclusivity monitoring as mandated by DPCA. FDA recommends routine monitoring of adverse events for this drug in all populations. Does the Advisory Committee concur?

I'd like to acknowledge the members of the Office of Drug Safety and the Division of Special Pathogens and Transplantation Products for their help in this presentation. Thank you.

DR. NELSON: Thank you. Questions, starting with Victor.

DR. SANTANA: Point of clarification; the most common pediatric adverse event was hematologic but you did not give us details about those and --

DR. SHAPIRO: I actually have those for the committee.

DR. SANTANA: Can you briefly describe those and, as a corollary to that, and it may come out when you mention those, were those underlying

hematologic diseases that patients may have had that got worsened by the medication?

DR. SHAPIRO: Okay, the -- basically this was throm -- there were events of thrombocytopenia, hemolytic anemia, pancytopenia, neutropenia and coagulopathy and you know, most of these patients had underlying problem with, you know, that -- you know, mainly Ciprofloxacin was used -- had been used in fairly sick patients.

DR. SANTANA: Do you know if any of those patients had underlying hematological or oncologic problems?

DR. SHAPIRO: I would just have to double-check that for a moment. Joette, do you know?

DR. NELSON: While you're looking, are there other questions?

DR. SHAPIRO: Okay, there was one patient who had basically liver disease who had enterococcus faecalis and staph aureus infection. So this was a liver transplant patient, so you wouldn't expect to have hematological issues because of their liver disease.

The other one was a patient which we -- had a recent history of meningitis but this was one that had neutropenia anemia and Coombs positive, so

would not -- you know, this could be secondary to infection. The other patient was a patient with Down Syndrome who was receiving other medications. He developed a low fibrinogen and -- well, with rising thrombin clotting times. So this was a patient underlying condition with a lower respiratory tract infection.

DR. NELSON: It occurs to me an interesting epidemiologic question would be to look at the trends in off-label use of antibiotics over time, because one hypothesis I would have is given the increasing resistance that develops over time and also the lack of other drugs sort of in the pipeline, something like Cipro, at least in my experience, our infectious disease consultants start recommending it when we get down to where we've tried everything else and I suspect what we're seeing here is the patient population who is very ill that we then try Cipro in, and I wouldn't be surprised if that trend would be seen in all antibiotics at some point as we need to continue to escalate into second and third line drugs as we get more and more difficult patients with infections to treat. So that would at least be my interpretation of what we're seeing in this data and I suspect that would be almost true of any antibiotic

that we would be evaluating.

DR. SHAPIRO: I would have to concur from my own experience, but I would have to say that some of the indications here for the 17 adverse events I summarize here, one was UTI prophylaxis which I would definitely not consider is something I would use Ciprofloxacin for. Another one was a febrile episode, not my first choice and for cases of osteomyelitis, yes, it can be used but usually, you know, we try to use other antibiotics and these are the patients who usually go home on home IV. So I'm just trying to give you an idea. And also sinusitis it's not usually our first choice either or meningitis prophylaxis is a CDC recommendation for adults, you know, for someone who's exposed to Neissderia meningitides, but it's not include -- it's not an official recommendation. It's not labeled.

DR. NELSON: And the age of that patient that -- and I think many pediatricians will look and figure, you know, 13, 14, 17, what's the difference. So -- Ciprofloxacin is a lot easier than rifampin.

DR. SHAPIRO: Oh, yes, quite a bit, compared to four doses of rifampin. I would -- I'm just giving you an example.

DR. NELSON: Especially Ortho Cyclen or

something like that. And for urine tract prophylaxis, I mean, if the patient had just finished a complicated UTI with a very difficult to eradicate organism, some physicians would consider that good practice to go ahead and continue them on that Cipro at that point. That may be wrong, okay, but I think some might do that.

DR. SHAPIRO: Well, as Larry mentioned, my background, I have a little background in nephrology. I can tell you that, yes, we've had patients who have constant Pseudomonas infections, the concern is that when you're using it for a prophylaxis with Ciprofloxacin, out concern has always been the development of resistance. It's not our favorite drug to use for prophylaxis.

DR. NELSON: So before seeing if we concur, are there other comments or questions? So the recommendation is that this also be relegated to the routine but yet vigilant monitoring going forward. A show of hands for those in favor of that. Any objections or abstentions? Let the record show that all hands of voting members were raised. Thank you.

DR. SHAPIRO: Okay, I'd like to reinvite Solomon Iyasu to the stand who will continue the discussion.

DR. MURPHY: Dr. Santana, in your thing on page 219 and 20 are the heme cases, just so you'll know they're there. Okay, if you want to look at them.

DR. SANTANA: What page did you say?

DR. MURPHY: 219, 220.

DR. SANTANA: Thank you.

DR. NELSON: Now, before Solomon gets started, let me comment, the next four that are being discussed are part of now the abbreviated presentations, so the goal here is to get through all four of them and then talk about them as a group. Now, if there is a point of overwhelming concern after one of the abbreviated presentations, feel free to scream and we'll recognize you but the goal is to go through all four and then discuss them as a group.

DR. WARD: What did we decide on the label to be in our previous discussion number 2?

DR. NELSON: Cipro?

DR. WARD: No, Detrol. We voted on a routine monitoring but --

DR. NELSON: Right, it was the labeling as presented and as read by --

DR. WARD: Okay.

DR. MURPHY: I mean, we will take back the

recommendations that Rosemary and I, sidebar here, you know, that the committee would encourage, you know, inclusion of confidence intervals, where we can, where we have that kind of information. And as far as that label is concerned, I think the concern about the word "higher", all I can tell you is the medical officer wrote down your concerns and we'll probably take them back to the division. One of the issues here is that -- and I just want to state as a fact, the labels are negotiated and the negotiation has occurred. Clearly the company is not going to fight taking out something that says it's higher, so I think that won't be a big issue if the Division feels they're comfortable with taking the recommendation. So if your question is, will we make sure that that recommendation is translated back to the division, the answer is, ?yes.?

DR. WARD: Right, I think that's as much as we can ask for. The other would be in place of percentage to actually have the numerator and denominator so that again, we could evaluate or judge how big of a sample we were dealing with.

DR. MURPHY: Right.

DR. NELSON: Tom?

DR. NEWMAN: I would like the Pediatric Advisory Committee to strengthen your hand in those

negotiations by unequivocally saying we want -- you know, point us to the confidence intervals for the efficacy data, not just the adverse effect data.

DR. MURPHY: Well, that's what I was referring to, because that's more likely that we'll have that, I mean, definitely, so we will go back with the fact that you would like to see that in the -- particularly where we have -- let me put it this way, they tend more likely to put it in when you've got a positive, but you also want to see it where we have the negative.

DR. WARD: Actually, it's very important for negative studies, too.

DR. MURPHY: I understand. We've gone from nothing to more and I'm just trying to -- you say you think it's very important, also for the negative information.

DR. NELSON: And start to require packaging of magnifying glasses in with the labels. Solomon.

DR. IYASU: Okay, now we've come to the last part of this session. I'm going to quickly go over these four drugs and summarize for you why we think there are no safety issues raised by the review and that we're going to ask you that these drugs will

go back to the routine monitoring. I want to recognize a few people who are present here for these reviews. For Zemplar, the Division representative is Dr. Eric Colman, who is actually there in the back. The Medical Officer from the Division of Pediatric Drug Development who reviewed this drug is Alan Shapiro, who was just here. For Zomig, it is Eric Bastings from the Division of Neurology Products and the Medical Officer from Pediatrics is Dr. Susan McCune who is sitting in the back there as well. And Trusopt was -- the Division representative from Anti-infectives and Ophthalmology Drug Products is Dr. Rhea Lloyd and the Medical Officer from the Pediatrics is Dr. Jane Filie and Dr. Jane Filie also has done the review for Arava for pediatrics and the division representative is Dr. Carolyn Yancey. So if there are any follow-up questions for details, we have adequate resources to respond to your queries.

First, I'm going to discuss Zemplar, which is a synthetic Vitamin D analog. Its sponsors, Abbott Laboratories, indications for which this drug is approved is prevention and treatment of secondary hyperthyroidism associated with chronic renal failure. The original market approval was in April of 1998, exclusivity was granted in December 2003. During the

one-year review there were no pediatric adverse events that were reported through AERS and also looking through from market approval through January 2005, there were no pediatric reports of adverse events. It is estimated that approximately 1,000 pediatric dialysis patients may be exposed to the medication. Primarily, this is used in clinics and so the outpatient use is very limited. Safety and effectiveness were examined in a 12-week trial in pediatric patients with end-stage renal disease on hemodialysis and the details of this study are described in labeling and you have that in your package.

I must point out that there were no patients in the trial that developed hypercalcemia and that is also indicated in the label. In summary, for that drug, there are no safety concerns so I'll ask the question of the committee at the end of the presentations for all these drugs.

The next drug is Zomig tablets and Zomig ZMT, which is an orally disintegrating tablet. It's a selective 5-hydroxytryptamine receptor agonist sponsored by AstraZeneca. It's approved for acute triptodemigraine with or without aura in adults, not recommended for pediatric use; however, the

information from exclusivity studies is in the label and that is in your package. The original market approval date was November 25th, 1997. Exclusivity was granted on December 18th, 2002.

Turning to the use in pediatric patients, pediatric patients accounted for less than two percent of all claims for Zomig oral tablets and five percent of all claims for Zomig ZMT, so the use is not that great. During the exclusivity period -- post-exclusivity period, there were two pediatric adverse event reports identified. One was an accident of ingestion of a 2.5 milligram Zomig by a toddler. He was hospitalized for observation. No adverse reactions were noted during that hospitalization episode but it's what's in the AERS report, so that is the reason why we're reporting that to you.

The second case in an adolescent was partial seizure after taking Zomig. The patient had a history of seizures following astrocytoma removal that were not being treated. At that time, this patient was not on any anti-convulsants. The partial seizures are unlabeled but unclear if they are due to the drug or the underlying pathology.

We -- but looking at the adverse event reports prior to the exclusivity period, there were a

total of 24 reports. There were two reports of death; however, upon cross examination, they represented the same patient, so there's really one, both of the same patient was an intentional overdose of Imitrex, Zomig and Sudafed, so a confounded case. During this prior reviews there were certain unlabeled events that occurred in the frequency of less than two or three dose now drug ineffective lethargy, accidental exposure, accidental overdose, brain edema or pupils fixed, not that the brain edema and pupils fixed were only noted in the intentional overdose patient.

There were no new concerning unlabeled safety signals identified in pediatric adverse -- in pediatrics from market approval to 2005. Therefore, we didn't feel that there was a safety signal that needed to be followed up. For Trusopt which is the third drug, it's a carbonic anhydrase inhibitor, marked by Merck. It's approved for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. The original approval was in December 1994. The exclusivity was granted in January 5, 2004.

For this drug, Trusopt, there's minimal use in pediatrics, .5 percent of prescription claimed for Dorzolamide, hydrochloride, ages 1 to 16 years.

There were no adverse event reports during the one-year post-exclusivity period and we concluded that there were no new safety signals that were identified through this review.

The last drug to be reviewed is Arava, Leflunomide. It's a immunomodulator marketed by Aventis. It's approved for the treatment of rheumatoid arthritis in adults, specifically to reduce signs and systems and to inhibit structural damages as evidenced by x-ray erosions and joint space narrowing and to improve physical function. The original market approval was September 10, 1998. The market -- the pediatric exclusivity was granted on November 10th, 2003.

The summary pertaining to the exclusivity trial for Arava is on the label but in summary, no pediatric indication was given for this drug because it failed to win on the primary endpoint. The trial with the superiority design against the high-dose methotrexate was all Leflunomide showed some activity over historical baseline, it failed to win on the primary endpoint. And you must realize that JRA is a very difficult disease treated by specialists, a complicated course, and the details and results of the trial and the PK section of the labeling are

adequately described. I think it's in your package as well. If there's further discussion about that and questions, I think we can address that as well.

But in terms of use in pediatrics, remember I said it's not approved for pediatrics. The minimal use in pediatrics, again, .1 percent of all prescription claims for Leflunomide were in pediatrics. There were two adverse event reports for the one year post-exclusivity period. One was a transient elevation of liver enzyme which is an expected labeled event. The patient recovered.

There was a second adverse event which is liver failure after intentional overdose of acetaminophen while on Leflunomide. The symptoms resolved and our conclusion is that there are no new safety signals that have been identified through this one-year review. This completes the review for the four drugs and we recommend that these drugs go to return monitoring for adverse events. Does the Advisory Committee concur with this conclusion?

DR. NELSON: Thank you, Solomon.

DR. IYASU: And I would like to acknowledge all the collaborators in this review from Office of Drug Safety and from the Office of New Drugs, and there are many of them. I think I'll just

keep the slide for a couple of minutes. Thank you very much. If there are any questions, we have also the medical officers from the Review Division and from -- and I'm here also to answer any further discussion about these four drugs and our conclusions.

DR. NELSON: Questions or discussion? That slide impresses me by the amount of work that goes into producing even the abbreviate reports.

DR. IYASU: Right. We have to go through the whole process before we reach that conclusion and I want to recognize not only the Office of Drug Safety and the Review Divisions but also certain individuals who are not named usually in these presentations, who work very hard to make this happen, and Kristin Phucus is our project manager who has been very instrumental in organizing and coordinating among the different offices to get these reviews done in time and could you stand, Kristin and be recognized?

And there are many more other in the Division who help us. And all the medical officers within the Division do spend a lot of time, including our leadership here, Dr. Rosemary Roberts and Shirley Murphy and Lisa Mathis, where is she, who work very hard with us reviewing these drugs. And it's a tremendous amount of work. If I was to estimate the

number of people involved in these reviews for the eight drugs it would probably be 100 people across the different offices.

DR. NELSON: Okay. So I guess the question is, do we concur that these four drugs can now be placed under routine monitoring? So hands of those that would be in favor of that recommendation. Any objections or abstentions? Seeing none, let the record show that all voting members' hands were in the air, in favor of that. Thank you, Solomon.

DR. IYASU: Thank you very much.

DR. NELSON: And Dianne, the agenda says concluding remarks.

DR. MURPHY: So now you all have experienced a transition. We started with sort of our standard review, we went to this abbreviated, and tomorrow we will be discussing a product which -- what we were calling a focus expanded presentation and which we have brought in other people to also make presentations. And certainly I think we need to do this a couple of times and circle back and see how useful the committee is finding this approach or not.

I do want to emphasize that we do send you this material as soon as we get it cleared and we tried very hard to separate out the Subpart D stuff

for the committee because we knew the committee would want to see it, so that you would get that earlier before you got drug stuff and at least have time to look at some of that. And we are now trying to get, as you know, not only the ODS reviews, which we think are extensive, as you can see, and go into tremendous background, but also the slides, so you understand somewhere about what we're thinking. So -- but the ODS reviews, you should always be getting and have time to read before you get here. Okay? Our slides, you may or may not always get. We try to get them to you before the review, but as I said, this is an evolving process and we will continue to re-evaluate it but we look forward to your participation tomorrow and I really don't have anything else to say except for I appreciate everybody being here and appreciate the feedback that we got back from you all today on the products that were presented this afternoon.

Rosemary, Solomon, anything else?

DR. ROBERTS: I would like to point out in your notebook on page 480, the labeling that has gone into Leflunomide with respect to the study. This is -- this is really FDA going out on a limb to put this kind of information in a label. This particular study is -- as Solomon has told you, was a superiority

design. And Leflunomide was studied against a high-dose methotrexate and so it did not show superiority against high-dose methotrexate. Now, and Carolyn Yancey, who is the pediatric rheumatologist, who knows more about this than I, but it's my understanding that to see an efficacy with methotrexate of 89 percent is really very high. And the efficacy seen with Leflunomide was 68 percent, which in some trials with methotrexate would be what you'd see with methotrexate. And it's my understanding that with no treatment it's somewhere in the 30 to 35 percent range. So although Leflunomide certainly is not a drug without adverse side effects, nor is methotrexate, and the juvenile rheumatoid arthritis patients that are having to use drugs of this nature are those who really do need anything that could help modify their disease.

So after long talks with the Division, and this had been -- this subsequently was brought before a regulatory briefing, we did agree that it was very important information to let the prescribers of drugs like this for special populations to be aware that although it failed on the primary efficacy end point, there was activity of the drug.

So I just wanted to point out that this is

-- this is really new for the agency and if you all had any comments as to whether there's more we could do, less we could do or what.

DR. NELSON: Let me just ask a couple quick questions myself and then go to Mary and Tom. As a non-rheumatologist, I wouldn't know that the active comparator was methotrexate, so at the first glance, unless one is in the know about the design of the trial, you wouldn't actually know what it was compared against. The second is, as a non-statistician, if I knew it was designed as a superiority trial, having listened enough to the debates about choice of difference, et cetera, I would then ask myself, well, what's the confidence I can have that it was equivalent? I mean, if what you're saying is that 68 versus -- that may be close enough that it's better than nothing, is there some way you could equivalence so that actually I conclude that it's not ineffective, but yet it's effective because it was compared against something that just happened to be really good in that trial?

So as it says, I mean, I think it's -- I agree that this is a step forward, but it still leaves a couple questions in me as a sort of naive consumer, non-rheumatologist?

DR. ROBERTS: Well, I agree with you that it leaves questions open. For the physicians with the expertise who are taking care of these patients, they can probably put -- fill in some of that missing information and I have heard criticisms that there is no dose put in and things like that, so how helpful was it really? As I said, this is our first launch out into doing something of this nature and I think that we actually did this before we had the buy-in of the entire center as to moving towards this. And it was presented and I think there was agreement that we need to try to inform as best we can, if we think that there is a product, especially in a special population, where there is potential use of that, and let those specialists be aware of that.

DR. NELSON: Mary and then Tom.

DR. YANCEY: I'm Carolyn Yancey. Just two comments. In terms of the dosage and the information we've put in the PK section of the PK section of the label, if you look at that carefully, you'll see we describe the entire study group with children based on weight and that was an analysis that took place within the Division, not from the sponsor. They submitted the analysis based on age which pediatricians certainly recognize in a chronic disease that

certainly is not going to give you informative information.

The other issue that came up with the information that came from that internal analysis was the fact that it looked as if the children who weighed less than 40 kilograms were under-dosed. We were extremely careful and we vetted this in many arenas. It looked as if they were under-dosed. In terms of the outcome, the advocacy outcome, 68 percent for a DMAR, a disease-modifying anti-inflammatory, anti-rheumatic drug is significant. If you look at adult studies for DMARs you will typically get an outcome of 30 percent, possibly 40 percent and that would be outstanding. So to see methotrexate, which we know does very well in children, that's not new information, but to have the outcome of the drug under study at 68 percent was outstanding and to Rosemary's point, this was the first time we really pushed to get the clinical information from the pediatric trial into the label when, in fact, the sponsor -- I want to make this clarification from the slides, did not request an indication in children. This was also a very unique situation, which preceded pediatric involvement being in that rheumatic disease group, so a very challenging label.

We do not list the name of an active comparator unless the sponsor has submitted and succeeded with two efficacy trials and that may be debated, but we have been extremely careful in rheumatology not to list active comparators. This came up with another drug, quite familiar, got a lot of press since September and we did not list the active comparator because they, in fact, did not achieve what needs to be achieved to put that in a label from which they can then market that advantage.

DR. MURPHY: I think that's a really -- I was hoping you'd say that, because the whole concept of putting active comparators is just --

DR. NELSON: It's a reverse kind of marketing. I understand.

DR. MURPHY: Yeah, exactly, exactly, exactly.

DR. NELSON: Mary and then Tom and then Bob.

DR. GLODE: Based on what you just it may not apply to this drug, but maybe it will apply more generically. If you're putting together a pediatric exclusivity study, and you're trying to decide, is it the sponsor or the FDA or both together who decides whether or not the design is a superiority trial or a

non-inferiority trial? Who determined they went for superiority instead of non-inferiority?

DR. MURPHY: I'll answer generally and let you answer for this. The -- for just routine drug development, the company, theoretically could go out and do anything it wanted and show up on our doorstep. Okay? They usually come and visit us and talk to us and we talk about what we recommend. Sometimes they take those recommendations, sometimes they do not. They do not have to. They can design the trial they want. Now, for exclusivity, however, if it is a written request, then we say what trial design we want and I --

DR. YANCEY: Correct. That was vetted with the Division and the sponsor and the sponsor wanted a superiority design trial with the feeling based on the literature as well as the performance of the drug under investigation in other populations, specifically adult. They felt as if they potentially could succeed with that statistical design.

DR. NELSON: Tom?

DR. NEWMAN: Well, I think generally more information on the label is good. I particularly do appreciate the confidence intervals here. One suggestion would be, I had to spend a long time

looking at it to tell what the confidence intervals were of because there's no point estimate there and so normally they don't overlap zero, they don't overlap one. I'm trying to tell because -- so one suggestion would be to make it clearer what that is and it looks like it's the improvement in this change in functional ability, which is measured in unknown units, so I don't know whether point one and point two is a big change or a little change.

So something, either whatever the standard deviation for this measure, something to let me know whether point one or point two is clinically significant and something to indicate that that's what this confidence interval is of would be helpful but I appreciate -- I think that when these studies are done for exclusivity, in general, the goal should be to have the written request be for something that then would be able to be put on the label, that it will be that well done and that important that then, you would want to put it on the label.

DR. NELSON: Thanks, Tom. Bob?

DR. WARD: What goes in the label is clearly a moving target over the last decade and this is, I think, a very well-presented amount of scientific data but I would wonder if the network of

rheumatologist, for example, if they were presented with this, what their reactions would be, what their questions would be and would it communicate effectively to them. And that's a network that is accessible to you and I would suggest it doesn't -- somebody doesn't even have to be there but it could be simply mailed to them with a question about what are your questions, does this communicate to you? Do you feel you can prescribe for this population that's very difficult to treat more effectively with this label?

DR. MURPHY: Bob, so you're asking us to mail to the group for a label -- for something that would not indicate it.

DR. WARD: Correct. But it may not be indicated but when you look at the comparison to placebo, it would appear that it is a very significant improvement. And I don't know the side effect profile of Arava compared to methotrexate well enough to say, "Gosh, I think this might be safer and therefore, I would be quite happy with let's say a 68 percent response rate with Arava rather than going for an 80 percent response rate in methotrexate. But I would just wonder if the population that needs to use this information if they would feel that this was a really effective presentation of data to them. That's what I

was thinking.

DR. YANCEY: In response to that, actually the information that was put into the PK section of the label was put in there because of that reason.

DR. WARD: Great, okay.

DR. NELSON: But I would also speculate that if you sought that advice, it would, A, have to be in a public forum and B, if you asked more than nine, it would have to go through the Office of Management and Budget; is that correct?

DR. WARD: At 11 you go to the White House, I think.

DR. NELSON: Dr. Gorman.

DR. GORMAN: A point of information; on the summaries for these studies that goes on the FDA website, would the active comparator be named and would the detailed information that Dr. Ward so desperately wants shared with the rheumatologist be available?

DR. MURPHY: The answer is, yes, I would hope so but the definition of summary, if you go up there and look, varies but yes, there should be a very thorough description of the trial and the outcomes and the adverse events and pharmakinetics.

DR. GORMAN: So perhaps Dr. Ward could

just e-mail then the hyperlink and say they could look at it for their information.

DR. WARD: I'll do that.

DR. GORMAN: I knew you would.

DR. NELSON: Judith.

DR. O'FALLON: Just this business about the superior or the versus non-inferiority trials, it takes a lot fewer patients to do a superiority trial than a non-inferiority trial and so especially when you guys are not requiring that they show efficacy. The smart thing to do is to do a superiority trial because you can do it with far fewer patients than if you're going for a non-inferiority. And the reason is that in superiority you're looking for big difference and for non-inferiority trials, you're looking for little differences and if you're looking for little differences, you have to have big samples. Okay? It's counter-intuitive but that's the way it works.

DR. NELSON: And the answer to the question was, yes, methotrexate is named in the clinical summary. So it might have been raised the question whether you should put the website on all the labels, you know, the general website.

DR. MURPHY: Actually, that's a very interesting thought.

DR. NELSON: Yeah, I mean, you know, just where to find it.

DR. MURPHY: Yeah, because there is so much more information for the very few pediatric studies that we have, yeah.

DR. NELSON: Mary, do you have a comment?

DR. GLODE: Well, just in response to Judith's comment, but if you go for superiority and you lose, you might wish you had gone for non-inferiority.

DR. NELSON: Victor?

DR. SANTANA: So I have hopefully a last question since we're a little bit over time here. And it has to do with -- maybe I was asleep when this was discussed earlier in the day but now we have three categories that we're going to put these adverse events into and then depending on the category, there will be a deep discussion in the committee or not. And I think it's intuitive the last one, right? I mean, abbreviated presentations, nothing new there. But I'm not sure that I understand the thresholds or the criteria that define the first two and how does -- what is the new word, how does a standard then become an in-depth or, you know, can you clarify for us in public what criteria you're using to define those two?

DR. MURPHY: Well, I can clarify the first two in that what we decided upon in our review, our discussion earlier which is those products where we think we see something possibly, we are going to bring those in -- for the adverse event part now, we're going to be bringing those in for discussion and try to focus on those where we think there might be something. The other we just described. What happened in this process, and Solomon can speak to this in more detail, is we may or may not want to keep doing this sort of in between thing. In other words, we were trying to also provide you additional information. That was one of the things, I think that went on here and Solomon can speak to what other criteria we used to decide to give you this one that was in between.

DR. IYASU: Well, I think whenever there's a clear suggestion from the reviewers that there is a potential safety issue, we're going to try to give you whatever information we have, as much detail-extensive information so that you can make some informed decision or advice to us. You can define maybe potential safety issues in many different ways but you know, we're concerned enough because it's either unlabeled and it's occurred in pediatric patients

where -- and the severity may be higher or the frequency may be higher than what one would expect.

And if this was known to the pediatric -- to the prescribing community, this safety issues, it can potentially influence their prescribing habits. Those are some of the things that may go into the -- into some of the factors that we take into consideration but basically it's the post-marketing interviews that we have and in the context of what we know from the clinical trials. Now for the standard presentations, this is sort of what Dianne is saying is in between. Is there something that we would like to get some discussion on or inform you about new developments?

For example, for the Detrol issue, it was really the FDA's approach to addressing the safety issues raised by the prior year reviews and say, "We're taking some action on this", and really informing you that we've done some active labeling and we've started the process. So that is an important communication piece that needed to get out in the public domain and also get some input from you. For Cipro, as I say, I think in my presentation it wasn't more -- sort of a safety -- new safety issue. It was really a question of the severity. A very commonly

prescribed drug. These are the range of things that we're seeing in the AERS report and maybe there are some knew insights out there that the committee can provide into this and so we decided to bring you this review because it's really a very commonly prescribed drug and we don't know how people know about this but not everybody knows about some of the severe cases that we saw and the fact that the context in which these reports have occurred has been for off-label use.

DR. SANTANA: And so what bumps you to an in-depth?

DR. IYASU: The in-depth is what I say, is like what I described first, that it has to be important enough and concerning enough that you know, if that information is known for example, and it's discussed and prescribers have that knowledge, that it might actually influence their prescribing habits. But really it's based on the available data that we have. We're not usually making causal inferences based on post-marketing. But there is a concern here that we wanted some input from you.

DR. MURPHY: Let me try it another way. I think what's happening is that what you heard that in between what we're calling sort of the standard

overview are parts that we might lump into the abbreviated but we thought because this is a pediatric advisory committee involved with safety, if there was some activity that had gone -- already happened or was of interest that we, instead of our first time out, if you will with this new approach, we thought we would rather bring that to you and tell you we didn't really see anything or it already had been noted and taken care of and put in the label and inform you of it. So this is a group that, as I've mentioned, we're not really sure and you all -- we'll get feedback from you what we should do with it. Maybe we should put it in the abbreviate because we're not telling you we're seeing anything in the way of a safety signal.

DR. SANTANA: I asked the question because I'm speaking now as a public consumer who also uses medications and things like that. I was struck, as you well know, that there was an article in the Wall Street Journal this morning about what we're going to discuss tomorrow and so when I read that article based on what I've reviewed trying to come here, I was trying to weigh the judgment of why this particular medication that we're going to discuss in-depth, got bumped up to the next category after hearing everything that was presented today. And so as a

public consumer, I want some clarity how the agency, in terms of what criteria they're using to define these as more in-depth, I think that would be a good point to put out there.

DR. MURPHY: I think --

DR. SANTANA: It's not a negative comment, it's actually a positive comment.

DR. MURPHY: No, no, I think Solomon summarized it, that we think we see -- we saw unlabeled new events. It's a very commonly used product. We think it might impact the way people at least discuss a risk management. You know, so I think -- is there a category I forgot, but, you know, we just felt that this is one we could tell you that there's nothing going on and we needed to bring it to you and do it in-depth.

DR. NELSON: Thank you. I might point out, in Victor's behalf, that his reading of the Wall Street Journal did not bias him in terms of participating in tomorrow's discussion.

DR. SANTANA: It's a public document, I paid for it.

DR. NELSON: I've also been asked, since we meet tomorrow at 8:00 a.m. in this same room, that those of us who have wrappers and other bottles that

we've consumed, if we could make sure that they find their way to a trash can so we have a nice -- and members of the audience, so that we have a nice clean room to come back to in the morning. So with that, I think we're adjourned.

(Whereupon, at 4:45 p.m. the above entitled matter concluded.)