UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
OFFICE OF THE COMMISSIONER

PEDIATRICS ADVISORY COMMITTEE

SIXTH MEETING

MONDAY,
FEBRUARY 14, 2005

The Advisory Committee met at 2:00 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, Consultant-Consumer Representative
JOHN WILLIAM MURRAY MOORE, M.D., M.P.H., Member
THOMAS B. NEWMAN, M.D., M.P.H., Member
JUDITH R. O'FALLON, Ph.D., Member
VICTOR M. SANTANA, M.D., Member
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

PRESENT FROM FDA:
LAWRENCE GRYLACK, M.D.
SOLOMON IYASU, M.D., M.P.H.
DIANNE MURPHY, M.D.
ROSEMARY ROBERTS, M.D.
HARI CHERYL SACHS, M.D.
ALAN M. SHAPIRO, M.D., Ph.D.

A-G-E-N-D-A

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

2:09 p.m.

CHAIR CHESNEY: I think we are ready to start. I want to welcome everybody to this afternoon's session on Adverse Event Reporting. I think we'll start by letting Jan Johannessen read the necessary things that he has to read before we start.

DR. JOHANNESSEN: I would like to read the meeting statement. The following announcement addresses the interest of conflict of interest with respect to this meeting and is made part of the public record to preclude even the appearance of such at this meeting.

The topics of today's meeting are broad applicability and, unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special Government employees have been screened for their interest as they may apply to the general topics at hand. The Food and Drug Administration has granted particular matters of

general applicability waivers for Drs. Chesney, Bier, and Santana which permits them to participate fully in today's discussion and votes.

A copy of the waiver statements may be obtained by submitting a written request to our Freedom of Information Office. Because general topics impact so many institutions it is not prudent to recite all the potential conflicts of interest as they apply to each participant.

The FDA acknowledges that 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 would 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.

We would also like to note that 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.

Thank you. We have open public comments scheduled at 4:00 p.m. and I would just remind everyone to turn on your microphones when you speak so that the transcriber can pick everything up. Thank you.

CHAIR CHESNEY: Thank you very much. Now I think we'll go around the room and have everybody introduce themselves and tell us what you do. We'll start at this end.

DR. GAROFALO: Sure. Thank you. I'm Betsy Garofalo and I am from Pfizer. I'm the industry representative.

DR. GORMAN: My name is Richard Gorman. I'm a pediatricians in private practice in Ellicott City, Maryland. I'm the chair of the American Academy's Committee on Drugs.

MS. KNUDSON: I'm Paula Knudson. I'm the consumer representative to this meeting and I'm the IRB Director for the University of Texas Health

Science Center in Houston.

DR. FANT: I'm Michael Fant and I'm an neonatologist on the faculty of the University of Texas Health Science Center in Houston.

DR. BIER: I'm Dennis Bier. I'm Professor of Pediatrics at Baylor College of Medicine and Director of the Children's Nutrition Research Center.

DR. DIAZ: Angela Diaz, Professor of Pediatrics at Mt. Sinai Medical Center.

DR. MOORE: I'm John Moore. I'm Professor of Pediatrics at UCLA Medical School and Director of Pediatric Cardiology.

DR. GLODE: My name is Mimi Glode. I'm a Professor of Pediatrics and Pediatric Infectious Disease Specialist at Children's Hospital, University of Colorado in Denver.

CHAIR CHESNEY: I'm Joan Chesney. I'm in infectious diseases at the University of Tennessee in Memphis and also the Office of Academic Programs at St. Jude Children's Research Hospital.

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

Committee.

DR. SANTANA: I'm Victor Santana. I'm a pediatric hematologist/oncologist from St. Judes Children's Research Hospital in Memphis, Tennessee. I noticed there was a Texas mafia over there. We have the Memphis mafia over here.

DR. O'FALLON: I'm Judith O'Fallon. I'm a biostatistician. I recently retired from the Mayo Clinic where I was working for 30 years in cancer clinical trials.

DR. NEWMAN: I'm Tom Newman. I'm a general pediatrician and Professor of Epidemiology and Biostatistics and Pediatrics at UC San Francisco.

DR. DOKKEN: I'm Deborah Dokken. I'm the Family-Patient Representative. I'm also currently a co-investigator for Pediatric Palliative Care Project and also serve on the Ethics Committee at Children's National Medical Center.

DR. MURPHY: I'm Dianne Murphy and I'm the office director for the Office of Pediatric Therapeutics in the Office of the Commissioner.

DR. IYASU: I'm Solomon Iyasu. I'm with

the Office of Pediatric Therapeutics and Acting Deputy Division Director for Pediatrics.

DR. ROBERTS: I'm Rosemary Roberts and I'm the Director of the Office of Counterterrorism and Pediatric Drug Development.

CHAIR CHESNEY: Thank you very much. I wanted to welcome the new members of the committee who weren't with us for the September meeting and people who just joined us today for the first time, or just named to us the first day. I was preferring specifically to Elizabeth.

I think Dr. Murphy has some introductory comments for us.

DR. MURPHY: Since I ran us over last time I've been told I'm going to be cut off at the knees. All I want to do is to welcome everybody and to thank you for being here and sitting through such an intense training session this morning. I appreciate your attention. I would like to say one thing. I want to reiterate that we are providing a recommendation to you but clearly we want your opinion. There are times when we go through the drugs that are upcoming but we

would make a recommendation where we weren't always as absolute so don't feel that we are giving you sort of an absolute recommendation. It's just where we think we are at this time on the need to do additional follow-up outside of the regular follow-up that you've heard about in your training session. That's the only thing I did want to emphasize. With that, I would go ahead and introduce Dr. Grylack, or would you like to do that, Joan?

Dr. Grylack is going to present our first product for review under the safety review that is mandated by BPCA, the Best Pharmaceuticals for Children Act. He is a trained pediatrician and neonatologist. He practiced neonatal medicine for many years primarily at Columbia Hospital for Women in Washington, D.C. and has clinical specialty interest in high risk infant developmental assessment and infant apnea. He has participated in clinical research and teaching. He's been with the FDA for two years and is finishing up. Are you now on your detail, Dr. Grylack?

DR. GRYLACK: I am.

DR. MURPHY: Okay. He's been in pediatrics for two years and now is on detail to the Division of Pulmonary Products. I'll turn it over to you.

DR. GRYLACK: Thank you, Dr. Murphy. It's a pleasure to be here and a privilege to be able to present a discussion on two drugs this afternoon. They are benazepril and esmolol. I will start with benazepril.

First of all, we have some background drug information. The drug appears as benazepril hydrochloride marketed as Lotensin. It also is in combination with other products, specifically benazepril hydrochlorothiazide marketed as Lotensin HCT. Thirdly, in combination with amlodipine marketed as Lotrel.

It is an antihypertensive drug and it's in the ACE inhibitor category of antihypertensive drugs. It is sponsored by Novartis and benazepril is indicated for the treatment of hypertension in patients greater than or equal to six years of age. Originally the single product was approved in 1991,

Lotensin, the Lotensin HCT in 1992, and Lotrel in 1995. Then pediatric exclusivity was granted in 2003.

There was a decrease in prescriptions for the single ingredient benazepril from the pre-exclusivity to the post-exclusivity period. Less than 1 tenth of 1 percent of benazepril and its combination products were prescribed for pediatric patients.

Based on our databases there was no pediatric use for benazepril or benazepril hydrochlorothiazide during the past three years. However, there were an estimated 5,000 mentions of benazepril amlodipine in the adolescent age group for the diagnosis of essential hypertension unspecified during the post-exclusivity period.

Let's look at the pediatric exclusivity studies. There were pharmacokinetics studies as well as efficacy and safety studies. There were three PK studies. The first one was a bioavailability study. It compared the extemporaneously compounded suspension with a tablet formulation in healthy adults. Bioequivalence was demonstrated in this study.

Secondly, the pharmacokinetics of

benazepril and its primary metabolite benazeprilat were studied after a single dose in healthy children and the results show that the main clearance for benazepril in children was larger than it was in adults.

Furthermore, the mean clearance of the active metabolite in school-age children was twice that of healthy adults and the mean clearance in the adolescent group was 27 percent greater than it was in healthy adults.

The third PK study was an open-label, steady-state study in 57 pediatric patients who were given multiple daily doses for five days. The results showed that the main clearance of benazepril was higher in the study patients compared to the healthy children and adults.

The main clearance of benazeprilat in children six to 12 years of age was more than twice that of healthy adults. However, in the adolescent population it was 27 percent higher than that of healthy adults. Finally, terminal elimination half-life of benazeprilat in pediatric patients who were

six to 16 years of age was one-third of that observed in adults.

Let's move on to the efficacy and safety studies. Investigators started with 107 hypertensive patients who were seven to 16 years of age. They were studied in a forced-dose titration study for four weeks. I've provided the definition of hypertension that was used as well as the dose range in the study. Of the 107 original patients 85 responded to the therapy during the titration phase and then they were enrolled in a two-week randomized double-blind, withdrawal, placebo-controlled study.

The primary efficacy endpoint was a change from baseline trough systolic blood pressure and the systolic and diastolic blood pressures in the placebo group increased by a range of 4 to 6 millimeters of mercury more than in the drug treatment groups. However, no dose response was observed.

The third phase enrolled 70 patients and this was an open-label extended phase and there were 64 completions of the original 70 patients. This study phase provided additional safety data. There

were no deaths in the safety study.

However, there were nine serious adverse events and I've listed the specifics of the SAEs here. In addition, there were nine discontinuations due to adverse events and, again, I've listed the types of events on the slide.

What labeling changes resulted from these exclusivity studies? First of all, clearance of the active metabolite benazeprilat in the six to 12-year-old age range is twice that of healthy adults and the clearance in the 12 to 16-year-old is 27 percent higher than the healthy adults. No dose response is observed among drug treated patients.

Thirdly, the recommended starting daily dose is .2 milligrams per kilogram and the daily dose of greater than .6 milligrams per kilogram was not studied. Treatment is not recommended in pediatric patients less than six years of age or in patients whose glomerular filtration rate is less than 30 mLs per minute.

Fifthly, pediatric adverse events are similar to those seen in adults. Sixth, the long-term

effects of drug on growth and development have not been studied. Finally, there are instructions for the preparation of the suspension formulation in the label itself.

Let's move on to the adverse event reporting starting with the period since market approval for the single therapy, the monotherapy with benazepril. What we have here is a listing for both all ages and the pediatric reports. Be aware there are notations here that the all-age listing includes reports with unknown ages and that both groups include, or may include, duplicate reports. In the pediatric age range there were five reports all of which were serious but no deaths.

Here I've listed the specific categories of adverse events since market approval, again focusing primarily on the pediatric age range. The underlined events or unlabeled events are also events that occurred in one patient. I've also listed the most common adverse events for the adult population as well.

Now, let's focus on the post-exclusivity

period. Again, we have it broken down into all ages and the pediatric population as well with the same notations about unknown age and duplicate reports. There were three serious adverse events in the pediatric population but no deaths.

The two unduplicated reports are described here. The first one was a four-year-old male with hypertension due to nephrotic syndrome and then hyperchloremic metabolic acidosis secondary to hypoaldosteronism was found after four months of benazepril monotherapy at .3 milligrams per kilogram per day. There was an improvement after reduction on the dose and there was complete recovery after the drug was discontinued.

The second case was a two-year-old male with a resolving viral infection. It was a possible accidental ingestion of benazepril as well as two other drugs. However, the doses of medications were unknown. The child suffered choking, coughing, crying followed by sleep and the outcome is unknown.

So, in summary, there is no pattern discernible in pediatric adverse events for benazepril

monotherapy. No adverse events were found for the combination products during the exclusivity period. This does complete the one-year post-exclusivity adverse event monitoring as mandated by the Best Pharmaceuticals for Children Act. The FDA recommends routine monitoring of adverse events for this drug and all populations and we ask the committee whether they concur in this recommendation.

Finally, we would like to offer our acknowledgements to all the individuals who helped in researching this drug in terms of the databases, the safety, the primary reviews. We thank them all for their contributions.

Next presentation, please. Thank you. The next drug I'm going to discuss is esmolol. Again, we'll start with the background drug information. It is marketed as Brevibloc sponsored by Baxter Laboratories. It's therapeutic category is beta-1 selective; that is, cardioselective adrenergic receptor blocking agent.

It is indicated in adults for the treatment of supraventricular tachycardia, intra-

operative and post-operative tachycardia, and/or hypertension. There is no pediatric indication at this time. Brevibloc was initially improved in 1986 and exclusivity was granted in 2003.

There was no change in the total annual sales of esmolol between the pre and the post-exclusivity periods. Ninety-nine percent of the total sales were to inpatient facilities and almost all of the inpatient use is in adults. Looking at the pediatric use there was less than 1 percent of pediatric discharges associated with esmolol during the pre and post-exclusivity period. Now, note that the post-exclusivity from which this data is collected was just a six-month period so it was not the full exclusivity period.

Moving on to the exclusivity studies, the pharmacokinetic/pharmacodynamic study was done in 27 patients with supraventricular tachycardia two to 16 years of age. I have listed the dosing here. And SVT was terminated within 10 minutes and 65 percent of the treated patients with the mean termination time of two minutes.

Moving onto the efficacy study, it was a randomized double-blind comparison of efficacy of three different doses. I've listed the doses here. The goal was to control intra and post-operative hypertension with repair of coarctation in the aorta. One hundred and 18 patients were enrolled from the neonatal period through six years of age. I've listed the efficacy endpoints there.

The results from the exclusivity study showed that systolic blood pressure did decrease in all dose groups but there was no significant difference among the groups in the change from the baseline values. Furthermore, there was no significant difference across the groups in the percentage of patients meeting rescue criteria or receiving rescue therapy.

Looking at the safety results 145 patients were evaluated and there were seven withdrawals the majority of which were due to hypotension. No deaths or serious adverse events occurred. However, 92 percent of the patients did have one or more adverse

events. These adverse events were consistent with adult labeling.

As far as the relevant safety labeling, most of the safety findings, as I inferred, appear consistent with current labeling or our known post-operative or post-procedural events. As a result, no new safety labeling resulted from the pediatric studies.

Moving on to the adverse event reporting, since market approval for esmolol we're using the same format in terms of reporting for all ages and pediatric reports with the same notations regarding unknown age and duplicate reports. There were nine serious adverse events in the period since market approval. Three of these were deaths and we were able to obtain data about these three deaths and I will discuss them.

The first case was that of a two-and-a-half-month-old female with coarctation of the aorta which underwent surgical repair and subsequent dilation. Then there was some unspecified surgery four days later during which supraventricular

tachycardia occurred and esmolol was given.

The blood pressure is described as bottoming out 12 hours post-op and then the patient was described as inflammatory response and expired. Concomitant medications were dopamine and fentanyl. An autopsy was done and necrotic tissue in the patient's heart and lungs was described.

The next case was that of a 16-year-old female who took an overdose of theophylline in a suicide attempt. Quite a high serum level. Tachycardia occurred subsequently and esmolol was given intravenously at the doses listed here. A grand mal seizure occurred after three minutes and esmolol was then stopped. Apnea and cardiac arrest occurred. Resuscitation medications were given. Unfortunately, there was irreversible coma and death.

The third patient was a five-year-old male who had surgery for hypoplastic aortic arch. He received nitroprusside for post-operative hypertension. Esmolol was added to the therapeutic regimen. Subsequent to the nitroprusside administration there were increased levels of cyanide

and thiocyanate. Nitroprusside was stopped and the levels of cyanide and thiocyanate decreased.

Reactions described in the report were "drug interaction" and "drug level" above therapeutic. Death occurred five days after surgery due to what was described as surgical failure.

Let's look at the most common adverse events since the market approval. The most common pediatric events, and these are listed as ones that occurred in the two to three occurrence range, the only one that's unlabeled is the -- sorry. The only one that's unlabeled is the urticaria.

The adult adverse event descriptions are also listed here and these represent five or more occurrences. As you can see, several of these are unlabeled events by virtue of underline.

Moving onto to the post-exclusivity period adverse event reporting, same format in terms of all ages of pediatrics with the same notations. There was one serious adverse event in the pediatric age range. It was not a death.

This single SAE represented a teenage

female patient who was undergoing osteotomy for correction of retrognathia. She received multiple medications during surgery. The normal preoperative vital signs were normal except for low temperature.

The reason I mention this at this point is that in the label it's stated that esmolol should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia. That's the point of listing the hypothermia here.

After 10 minutes of surgery there was an acute hypertensive crisis and sinus tachycardia for which intravenous esmolol was given. Pulmonary edema was seen on chest x-ray. Global ST segment elevation was read on the EKG. The laboratory result of elevated troponin level was obtained one hour port-operatively. This was thought to be indicative of myocardial ischemia. Surgery was halted. The patient stabilized and fortunately recovered.

In summary, there is no pattern discernible in the pediatric adverse event reporting. This completes the one-year post-exclusivity adverse

event monitoring as mandated by the BPCA. The FDA does recommend routine monitoring of adverse events for this drug in all populations and we ask the Advisory Committee whether they concur.

Again, acknowledgements to all the people who contributed to these reports. I would also like to acknowledge all my colleagues in the Office of Pediatric Therapeutics, Division of Pediatric Drug Development, and the Office of Counterterrorism and Pediatrics for their contributions. Thank you for your attention. I'll entertain any questions that you have.

CHAIR CHESNEY: Thank you very much, Dr. Grylack. Any questions from the Pediatric Advisory Committee? Dr. Santana and then Dr. Newman.

DR. SANTANA: Can you clarify something for me? In your first presentation on benazepril on slide No. 11 you made a comment that the treatment is not recommended in patients with a GFR less than 30 but you didn't give us any data in support of that recommendation. You gave us data in support of the other recommendations but not that one specifically.

I assume many of these patients were chronic renal failure patients who had hypertension. Can you clarify that for us, please?

DR. GRYLACK: Okay. I am looking for it and if anybody from the Primary Review Division wants to speak up in the meantime, feel free.

DR. SANTANA: It just struck me that was a very strong recommendation and I didn't see any data.

DR. ROBERTS: The reason for that recommendation is that patients with a GFR of less than 30 were not studied.

DR. SANTANA: Were not studied.

DR. ROBERTS: Yes. That's right.

DR. SANTANA: I got the sense from the slide resulting from exclusivity studies that there was data in support of that not because it was the negative. Thanks for the clarification. That's an important point.

DR. GRYLACK: Thank you, Dr. Roberts.

CHAIR CHESNEY: Dr. Newman.

DR. NEWMAN: Yes. In the slide just before that, which is No. 10, I guess the problem that

I'm having with both of these drugs is that it seems like they are given to pretty sick children who have a high frequency of bad things happening to them sort of at base line.

The inclusion criteria for the study of benazepril was only a diastolic blood pressure above the 95th percentile which is not a very strict inclusion criteria so I can't tell at all how sick these patients were.

It seems very difficult to tell whether this nine out of 107 rate of serious adverse events is any more than would be expected in this sick group of children without a placebo or a comparison group. Nine out of 107 for serious adverse events that lead to discontinuation of the drug seems high to me but I don't know what to compare it to.

DR. GRYLACK: Well, I agree that the definition for inclusion was just the percentile for height, age, gender and being off medication so that's certainly true. I don't -- I can't answer your question completely because, as you say, we don't have the comparison group. Again, if anybody from the

review division wants to comment on that, I would be happy to hear that.

DR. NEWMAN: I guess my concerns if the studies for exclusivity are supposed to be about safety, and these drugs, I think, in many cases are given to prevent bad things from happening, you know, hypertensive crisis, or whatever, or bad effects of hypertension. If, in fact, they increase the risk of those same events by a factor of two or three, would there be any way we would be able to know that from these studies?

DR. GRYLACK: You're saying if the frequency of the AEs were to increase two to three fold.

DR. NEWMAN: Yes, or even the events that they are designing to prevent. They are given not just because the blood pressure is high but because high blood pressure can cause bad things.

DR. GRYLACK: Well, I don't have information that looks longer term in terms of the sequelae of the hypertension so I can't answer that question. Certainly we know that growth and

development was not studied in this case.

DR. NEWMAN: I'm talking about catastrophes like cardiac arrest and the things that are being reported here, the renal failure and the hypertensive crisis and so on.

DR. GRYLACK: Presumably those would be reported if they occurred and then we do have a listing of whatever serious adverse events or discontinuations due to adverse events occurred.

DR. MURPHY: I guess what you're asking is are these trials powered to pick up a specific set of serious adverse events and the answer is no. I don't think that one can say looking at these numbers, particularly if you don't think -- you would have to go back and see what you thought had occurred in the adult which, again, I don't know if anybody from the division is here but that's the basis upon which the written requests are constructed, that you have a knowledge of what the event rate was in the adults.

You know the rule is to pick up 1 percent you have to have 300 so you know if you don't even have 300 patients in the trial that you're not going

to pick up something theoretically that is occurring less frequently than that. I think the answer is that the trials are based on what they think the event rate has been in adults.

If they think the event rate -- if they have some information that would make them think it would be higher or lower in kids and then that's the number that they will ask for. Should we be asking for more? I think all of us think it would be better if we could ask for more but in some of these trials, particularly where the Cardio-Renal Division has a dose titration option that they can use, then that gets to be a more difficult thing to do to have large numbers.

DR. NEWMAN: But I guess my concern in this case there were nine discontinuations due to adverse events. The sample size seems like it was adequate so it really isn't a question to me is this more than what would be expected from adults but is this more than what would have been expected in this group of children if they hadn't gotten the medication. It's hard for me to conclude that the

drugs are safe without being able to say that.

CHAIR CHESNEY: Dr. O'Fallon.

DR. O'FALLON: I'm having trouble evaluating the question for each of these six agents was -- treatments was. You are recommending that we go to routine monitoring and they are asking us do we agree and I'm having a major problem evaluating whether we have enough information here.

I was really -- I want to thank you for all the supplementary material that was sent to us. I found particularly the drug use information potentially useful. But I also read what you said about the limitations of the various databases you have available to you.

It seems to me that you do in most of these cases, not this one, not esmolol, this one I couldn't get any idea of how many kids have been treated with the stuff. I couldn't figure it out at all on the basis of what you had. In the earlier one there was information.

There was an estimate of how many prescriptions had been given to kids in that time

period. It seems to me that we need to have some idea of the quantity of information we have here before we can tell you whether we think you should stop now or go another year. This one, esmolol, I can't even tell what you've got.

DR. MURPHY: Well, I think in that situation you should make a recommendation to us that you want more specific information on the use. You want us to follow it and come back and tell you. You could tell us, "I want you to come back and I would like someone to look at what the rate is in this population before I can give you an answer on this."

I mean, you don't have to say, "Keep following it." You can come back and say, "We can't give you an answer not to follow it and keep following it until we get this additional information." Those are the things that we want to hear from you.

CHAIR CHESNEY: Dr. Glode.

DR. GLODE: If I can go back to benazepril and ask you a question. I'm having a little trouble distinguishing events from patients. Nine patients discontinued the drug, nine patients had serious

adverse effects, seven patients developed clinically significant laboratory abnormalities, and two cases had a severe increase in creatinine phosphokinase so that's 27 out of 107. Maybe those are repeating patients. It's the same people who discontinued it who had the adverse event who had the laboratory abnormalities.

DR. GRYLACK: Jan, I'm wondering if we can get that benazepril slide up. Okay. Thank you.

DR. JOHANNESSEN: Which slide was it?

DR. GLODE: I think I'd just like to know how many patients had one or more serious adverse event which includes discontinuation of the drug so I can figure out if I'm dealing with nine patients or 27.

DR. GRYLACK: You know, the different -- you know, the descriptions are provided here. They are separate groups.

DR. GLODE: But when you say, for example, hypertensive crisis is repeated in both of those so is that a patient had a hypertensive crisis that was called a serious adverse event and it also lead to

discontinuation but it's the same patient, John Smith? That's what I can't quite figure out.

DR. GRYLACK: Okay. Let me go back to the source here. Again, this indicates that there were a total of nine that discontinued as a result of AEs and then the AEs were listed and I presented that here. Then nine developed serious adverse events. Again, it doesn't indicate whether they were the same patients or not.

If the Review Division has any further information on that, I would be happy to hear that. That is what the report actually said in terms of the description. They did not say whether they were provided. I appreciate your concern.

DR. MURPHY: Okay. Larry, would it be possible? Do you have that data or maybe you can get back with the Safety Review people to see if they could tell you whether those are different or combined. Okay?

DR. GRYLACK: Okay. I can certainly do that.

DR. MURPHY: Could you please do that? I

don't know that we can separate it. Is it, Solomon? Do we?

DR. IYASU: Some of the information is actually in the package that you received. It's not probably as detailed as you would want it. In the clinical trial summaries that we get this represents unlike the post-marketing reports actual patients.

A total of nine but the description that you have under, for example, the second bullet is sort of the range of adverse events that were seen among this nine. We haven't given you how many were hypertensive crisis. In the detailed review there are actual numbers but it was considered to be not significant in terms of an individual event. This doesn't represent nine hypertensive crisis.

DR. MURPHY: No. What they are asking is are those nine -- if they discontinued because they were having serious adverse events, are these the same nine?

DR. IYASU: These are different nine.

DR. MURPHY: No overlap?

DR. IYASU: I don't think there's any

overlap.

DR. MURPHY: Well, we need to verify.

CHAIR CHESNEY: Can I just clarify? Your specific question for us is whether to return to routine monitoring based on the case reports you received for the first year post-exclusivity. In other words, we're given this background in terms of what happened with the exclusivity studies but our specific issue is whether the three reports in pediatrics received in the last year whether we are comfortable with that in terms of returning to routine monitoring.

DR. GRYLACK: Based on the information you received as well as the one-year post-exclusivity monitoring the three deaths, I don't know if that's what you're referring to, were not during the exclusivity period but they were since market approval.

CHAIR CHESNEY: No. I was looking at slide 15 which is the three pediatric reports no deaths in the year post-exclusivity.

DR. GRYLACK: Okay.

CHAIR CHESNEY: Do we need a vote on whether we -- or would you like a vote or is a hand count adequate or a general agreement?

DR. MURPHY: I think it would depend on whether it's close or not. If you have a general discussion and everybody agrees one way or the other, then we'll just say the majority. I think if it's close, then you better take a hand count. We'll just reinstitute whatever it is that you want us to do in the meantime. The only reason I say that, Joan, is that depending on what you guys recommend to us, it's maybe more difficult or less difficult to institute and we need to know the -- it's clearer. It makes it easier for us when we have very clear mandate.

CHAIR CHESNEY: Okay. Let me ask first with respect to benazepril does anybody have any other questions to ask? Yes, Paula.

MS. KNUDSON: I would like to ask will you describe to me routine monitoring versus what is the alternative monitoring.

CHAIR CHESNEY: Dr. Grylack. Dr. Iyasu.

DR. IYASU: Yes. Routine monitoring is

what was described to you this morning which means that the Office of Drug Safety will do their normal routine monitoring which means all expedited reports serious unlabeled events will be in their in-box. They will be looking at them as they come in.

Other nonserious labeled events will be looked at but they are not a priority area because they have to spend time looking at the serious unlabeled events without required reporting from the companies. There will be a focus on that. The rest of the reports that are nonserious will be looked at in a routine manner. That means if there is a safety issue they will go into the entire report for a particular drug but most of the focus will be on the expedited serious events.

Now, it is important to distinguish this because what we are doing right now there is a specific focus on BPCA-mandated pediatric adverse event review which means we are actually looking at everything that comes from that one-year post-exclusivity period so there is a big focus on pediatrics. In the routine monitoring will be all

reports irrespective of age.

DR. MURPHY: I think that the big point he's making is that generally they are not to pull out the pediatric population and look at it. I mean, certainly the pediatric report they will know is a pediatric report but it's focusing on the pediatrics with the adults as a background in contrast.

Plus everything else that the team tries to pull in, literature or whatever, and put in context of the trials that were conducted with kids because then they will go back and look at what happened during the trials, okay, versus the pediatric trials versus if you have a bunch of reports, mostly adults, some kids, and then what would normally happen within the division looking at that more likely in the context of the adult trials more than the pediatric trials unless there was a predominance to pediatric reports.

CHAIR CHESNEY: Does anybody else have questions? Dr. O'Fallon.

DR. O'FALLON: Just for clarification, these reports that we're looking at here came in

through AERS, right? Okay. So it's the passive report.

DR. IYASU: Yes. All of these post-marketing reports come in the spontaneous reporting system. You may hear it being referred to as AERS, Adverse Event Reporting System, or MedWatch system. They are one and the same.

DR. O'FALLON: They are all the same. So there is a serious question of under-reporting. Is there not?

DR. IYASU: Absolutely. That's one of the big issues that we will be discussing this afternoon later. There is a limit as to how much safety information you can pick up from post-marketing. Under-reporting is a big issue but also the quality of the reports that we get. To establish causality is really a daunting task.

DR. O'FALLON: I know.

DR. IYASU: There are many of these medications that are given in the context of other concomitant medications in complicated medical situations and it's very hard unless you have a

specific comparison group you are actually making measurements of everything that is happening to a particular patient and you know everything about the drug and how it's taken with dose. There's a lot of missing information. We try to make the most out of this limited information.

It's a good system, I guess, to pick up some rare serious events that you really can't miss. Then you try to examine it in detail and go back even to the clinical trials and see if there was any indication suggestive of like, for example, acute liver failure is one issue which often gets picked up by post-marketing.

CHAIR CHESNEY: Thank you. I think we are all very much looking forward to answering the bigger question and we need to try to stay a little bit on time here. We are already getting behind. Is there anybody on the committee that is uncomfortable with letting the FDA return to its routine AERS monitoring for benazepril?

DR. ROBERTS: Joan, let me just answer the question about serious adverse events overlapping with

discontinued. In looking at the report that you have it would appear that the hypertensive crisis is an overlap because it indicates it was discontinued. The hypertensive crisis resolved after discontinuation of the drug. The patient with that crisis was discontinued. Cases of acute renal failure and rejection of kidney transplants in two patients are an overlap.

CHAIR CHESNEY: Oh, sure. Okay.

DR. ROBERTS: If you look under benazepril --

DR. MURPHY: It's the one that says, "The Division of Cardio-Renal Drug Products" at the top. This is the summary that we talked about that gets put up on the web. Which page in there, Rosemary? Oh, this is to make it challenging

DR. ROBERTS: Okay. It is page 3 of the medical review. If you see the third paragraph down it talks to you about discontinuation secondary to AEs. The next paragraph speaks to serious adverse events. So, in summary, the hypertensive crisis is overlapped. The two patients with acute renal failure

and kidney transplant rejections are overlaps. The patient with abnormal blood creatinine the reason they were discontinued is because they had a history of a kidney transplant.

DR. MURPHY: So we think we see a future here where it would be helpful for us to indicate to you when they are individual patients that are new or different in these different sets of data.

DR. GRYLACK: Dr. Glode.

DR. GLODE: Back to being comfortable or uncomfortable based on, again, this medical review and the one we were just looking at, if you turn to the last page of that, I have to go into the category of uncomfortable myself because I agree with the medical reviewer who concluded that, "Benazepril seems to be associated with a number of safety concerns given the lack of information confirming the diagnosis of some adverse events," etc., etc.

The reviewer concludes, "The program under review is insufficient for the evaluation of safety of benazepril in the pediatric population." I agree with the reviewer. I think the information is insufficient

for the evaluation of safety. Since it's insufficient for the evaluation of safety and, if anything, there appear to be a lot of potential serious adverse events reported in 107 even though, again, not dealing with the post-exclusivity issue. I would think it deserves some increased attention.

DR. MURPHY: Okay. Let me just -- you think it deserves increased attention because? I'm just trying to articulate because one of the things we use is it's unlabeled. There's more than one patient that has a serious biologic plausibility. We're trying to make sure we can categorize in our head so we will maybe make the recommendation.

Your concern is that really for the limited number of patients you think there have been too many AEs and you think we need to look at more to make sure that we're not beginning -- that there isn't a trend that we're missing because we haven't looked long enough and don't have enough information in the original trial dataset plus the number of AEs who are coming in in this limited period of time.

DR. GLODE: Yes.

DR. MURPHY: Okay. Does anybody else support that opinion?

CHAIR CHESNEY: Can I just read the medical reviewer's recommendation? Remember that this was back in 2003, September of 2003. "Because of the aforementioned safety concerns and insufficiency of available data in evaluating the safety in the pediatric population, the supplemental application is approvable with the condition that the sponsor further evaluate the incidence of the observed adverse events and the nature of the relationship to benazepril in pediatric patients." What did that mean?

DR. MURPHY: I'm interpreting. I have to go back and ask for sure what it meant. Again, I don't think we have anybody from the Division of Cardio-Renal here which is something we will try to remedy in the future.

As you heard, the reports come in in a way in which pediatrics may not be specifically broken out and they are asking them to focus in on those reports and to make maybe additional comments and discussion on that. That would be my take on what they are

saying. You heard the periodic reporting may not separate out the pediatric issues and they are asking them to focus in on that report and tell them about those issues.

Rosemary, do you have anything else to add to that?

DR. SANTANA: I don't want to put words in Joan's mouth but I thought what Joan was trying to say was that there was a comment that this is approvable with the request that further information be looked at and brought to the attention back to the FDA so what happened with that new information? Is there new information? Is there further information that the sponsor has? You see what I'm getting at?

DR. MURPHY: Yes.

DR. SANTANA: That sentence leads you to believe that it was approved with the condition that the sponsor would give more information in the next two years.

DR. MURPHY: It is our understanding that we have presented to you all the information because we work with the division, the Cardio-Renal Division,

in obtaining that information. Is there somebody from Cardio-Renal or ODS?

MR. SCHLOTFELDT: Am I live? My name is Carol Schlotfeldt. I work for Novartis Pharmaceuticals.

DR. MURPHY: Oh, good. The sponsor. Maybe you can give us some clarification.

MR. SCHLOTFELDT: Maybe I can help the committee move on.

DR. MURPHY: But just so the committee will know, as far as I know, this is all the information we have unless this gentleman tells us otherwise.

MR. SCHLOTFELDT: Yes. The reference to "approvable" in this document refers to the fact that we were given an approvable letter at the time of the first action for this supplementary NDA. We subsequently provided the additional information that's referred to here about certain patients and that information was evaluated by FDA and we were subsequently approved.

Unfortunately, you don't have the report,

the medical reviewer's report, of her review of that supplementary information. But in her comments about the aforementioned safety concerns, "The supplemental application is approvable with the condition that the sponsor further evaluates the incidence of these events -- blah, blah, blah -- in pediatric patients referred to a certain subset of patients that had some characteristics that just weren't fully resolved in the original supplementary NDA."

DR. MURPHY: But that information was provided to the division.

MR. SCHLOTFELDT: It was subsequently, yes.

DR. MURPHY: This information we provided you is based on the information we got from the division plus information from Drug Safety.

MR. SCHLOTFELDT: Yes.

DR. MURPHY: Dr. Stockbridge, I see you're here. Would you like to add any clarity to this at this point?

DR. STOCKBRIDGE: I don't think I have anything to add.

DR. MURPHY: Okay. Bottom line is we think we have all the information that is available at this moment, because that's what we try to do, and have presented it to you.

CHAIR CHESNEY: So I think perhaps we have two choices. One is to ask the FDA based on concerns that have been expressed here to continue to look actively at the pediatric -- all the pediatric cases reported to the AERS system for another year, or to return to just looking at all the cases reported without necessarily singling out the pediatric cases. That's the two choices we have.

DR. MURPHY: Yes. And then report back to you which normally we would not do.

CHAIR CHESNEY: So let me ask --

DR. MURPHY: There's two parts to that really.

CHAIR CHESNEY: Right. For a show of hands of those who feel that what we've heard is disconcerting enough that we should ask the FDA to look closely at all pediatric case reports for benazepril for yet another year and then report back

to the committee. How many people would like to make that recommendation? Show of hands. I think that's the answer for benazepril.

Now we'll move on to esmolol. Questions about esmolol for Dr. Grylack. Dr. Newman.

DR. NEWMAN: Some of the same sorts of questions -- this is on your slide No. 7 -- where 92 percent of the patients reported one or more adverse effects and these were consistent with the adult labeling. Does that mean that the nature of the adverse effects was consistent or the nature and the frequency were both consistent? Again, it's hard without a comparison group to know how many of these things would have happened otherwise but that seems high.

DR. GRYLACK: Yes. The types of AEs were similar. We did look at one of the categories of hypotension and that was similar in terms of frequency but I can't say that all of the AEs were consistent in frequency. For that particular category it was similar but this refers primarily to the types of adverse events.

DR. MURPHY: Does that answer your question? In other words they looked at the really serious ones to make sure those were in the same range. You're concerned because it's 92 percent. Is that correct?

DR. NEWMAN: That does seem kind of high to me, yeah.

DR. MURPHY: Yeah.

DR. NEWMAN: Was it five percent in adults or 50 percent in adults? Again, since we don't have a comparison group of children, it's hard to know but it just seems quite high.

DR. MURPHY: It should be in the label.

DR. GRYLACK: Yes, we have the label here. Let's see. The cardiovascular symptomatic hypotension occurred in 12 percent of patients. The therapy was discontinued in about 11 percent, asymptomatic hypotension in about 25 percent. We looked at the pediatric frequency for that particular item and it was in the 25 to 30 percent range but I can't vouch for all of the AEs being the same in terms of frequency as in the adult labeling.

CHAIR CHESNEY: Can I make a comment about the label? I noticed for esmolol it says, "The safety and effectiveness of esmolol in pediatric patients have not been established." That's all it says about pediatrics.

DR. GRYLACK: That's correct.

CHAIR CHESNEY: And yet we have some safety information.

DR. GRYLACK: Well, there was no change in the safety labeling made as of this time.

DR. MURPHY: I think Joan's point is we had studies done. I think it was actually in one of the reviews a comment was made because it was not approved by -- I don't want to misquote this but they felt that putting in the pharmacokinetic data would be misleading, but your question is why wasn't there other information put in the label that at least studies were conducted and they were not found to have a dose effect.

CHAIR CHESNEY: It sounds like they haven't been looked at at all and, yet, we have information that it was looked at.

DR. MURPHY: Norm, I think I can be -- I don't think I'm stepping on anybody's toes to say that it is now Dr. John Jenkins who is the head of Office of New Drugs has now requested that the divisions take a more aggressive approach to putting this information in the labels.

Dr. Stockbridge, did you want to say anything else about it? Could you come up to a mike, please, for us? There. Thank you.

DR. STOCKBRIDGE: I'm Norman Stockbridge. I'm the Acting Division Director in Cardio-Renal Drug Products. The situation with this application was that there was really inadequate data from the trials that were done to address whether or not a clinically significant effect was achievable with the drug. There are several possibilities.

One is you do a trial and you find an effect you want to label it. It is also possible to decide that you ruled out an effect you would care about. We have recently put labeling into an application labeled for a drug where that was true. In this case it feel somewhere in between those cases.

The study was not adequate to conclude that just because it failed the drug wasn't useful. We were left with not much more information than when we started. The only thing we learned was you get out of 100 patients, or whatever it was, adverse events that sort of look like what you were seeing in adults. That's where the label sits.

DR. MURPHY: I think this is the same issue that has come up with the new reform in that, as Norm is telling you, we have to find ways of saying that we can't conclude that it worked or didn't work but that we can inform you that studies were done. We have to have better words in this statement and that's what we're trying to do now.

As I said, it's now policy that we are going to come up with some statement to indicate that studies were concluded. We were unable to determine that it did not work or that it did work and that's where they are on the situation.

CHAIR CHESNEY: Thank you. And that's fair.

Dr. Bier, you had a question?

DR. BIER: I guess, you know, most of us are relatively new at this and we have already come across this in the first two discussions so I guess it's going to come up again. If these were not pediatric studies and these were adult studies and we were hearing about five reports or nine reports or 13 reports, would that be sufficient in an adult study of a drug to establish -- to give us the information that we need here?

I mean, we are being asked if they are sufficient in pediatric studies. There shouldn't -- whether or not the quality and quantity of the information is sufficient to tell the signal from the noise shouldn't be any different. Where is the threshold for establishing this? I mean, obviously if everybody dies that's easy because you can tell there was an effect but, I mean --

DR. MURPHY: Well, Norm, because we are talking about cardio-renal I would appreciate it if you kick in after what I say. Okay? Fundamentally unless it's a pediatric specific AE, and we've mentioned, you know, it has to do with growth or has

to do with behavior, the learning, or something, or it has to do with something that came out and we've seen this where there was an adverse event that was not described at all in the adult trials.

Then in that situation clearly we are in a different realm than what's in the adults. Otherwise, if you just look at the adult trials, theoretically whatever the adverse events that occurred should be well described in the label from their trials.

If you are asking then what is the bar you have to pass after a product has been approved and it gets out there, it's the level of certainty that you have that it's a real signal with all the problems that you all have already heard about and that isn't going to go away. I mean, that's the problem here is how certain you can be.

Is there anything anybody can do if we put something new in the label when we're uncertain to better manage that risk until we are certain depending where you are on that certainly scale, or if there is something that we just don't think even though it's a few cases it makes sense from a biologic point of view

and we think it's not in the label and it needs to go in the label because it didn't occur at all during the trials and now we're seeing it, as we've talked about, those severe rare adverse events that occur after post-marketing.

Or we see that people are using it in different ways they are not supposed to be using it and we will go in and that's causing it. If we can link it to that, we'll put that in the label. I'm sure I'm missing something so anybody want to -- Norm, did you have anything to add to that particularly for cardio-renal drugs?M

DR. STOCKBRIDGE: No, I don't have very much to add. It is a real art to try to figure out what's worth putting in the list of adverse events. Very difficult even in controlled trials to figure out when a common event is more common.

Labels tend more or less to accumulate a lot of things in the also-seen kind of category where some of them probably have nothing at all to do with the drug and it becomes a list of things that you want a physicians to at least think about if they see it in

practice.

Yes, it's been seen before. Maybe that means you should think about taking somebody off the drug. Where anybody's threshold is for what to do and how many things to put into that list, that's really a very open issue.

DR. MURPHY: I mean, I'm just going to say this one more time. During a controlled trial we have a comparator. I mean, we can at least have something to compare it to. Here that's why we give you the control trial so you can see what went on there. Here it's trying to define what the background rate is in a population that isn't the population for which it's approved sometimes. That's why it becomes a art form.

CHAIR CHESNEY: Dr. Santana and then Dr. O'Fallon

DR. SANTANA: Dianne, my memory is not very good anymore. I don't remember everything but I think I remember a discussion we had in this committee, maybe a year, 18 months ago, where this same issue came up, as we do these exclusivity and pediatric studies when is there enough information

that it will mandate -- that's the wrong word -- what would be enough information that we should ask that the label be changed?

I remember the discussion went this way that there has to be a significant body of evidence that's well documented, etc., etc., in order to do that. I think part of that discussion included are their other mechanisms that the label could indicate that there are pediatric studies. I mean, they're not of the strength and the quality that maybe would mandate a complete change but to give the consumer and the practitioner an indication that there have been pediatric studies.

I even remember a committee member saying maybe they should be referenced to the FDA pediatric site that has all of these reports because these reports are published, am I not correct? They are out there already on your website.

DR. MURPHY: The summaries.

DR. SANTANA: Yes. I remember some discussion like this but I don't remember how we finally came to a conclusion on the issue.

DR. MURPHY: The "approvable" will not have anything but the summary. The other I think there is a situation where if it's approved you'll get the in-depth review. What I'm trying to say is I think we have turned that corner.

Just last month we had an e-mail from John Jenkins who is the head of OND saying we are going to put -- have to come up with a way of putting a statement in that these trials -- this is an older label so you guys are going to be frustrated with us for a number of more visits because there are a lot of labels that are coming to you that are done way back before -- 18 months before we bring a product to you.

One year for looking at the events, about six months to get it ready. We are going to have quite a few more labels that are going to come to you where there may be nothing in them.

DR. SANTANA: I guess my challenge to the group and to the FDA is to revisit this issue in a very organized way. When would we really have enough information that it would require that we recommend that there be an actual change in the label versus

when there is a body of information that has been gathered because of the exclusivity studies that we can no longer say in the label there are no studies because that is no longer a true statement but we don't feel comfortable enough that data is of enough strength that it should go in the label but the label should indicate it exist in some other resource that people can go to.

Those to me are two kind of complimentary points. As a consumer I do recognize I don't want to be scared with information that's not completely well studied and balanced but it's not also correct to say there is no pediatric information, Joan. We have to find a way to kind of marry both of those.

CHAIR CHESNEY: I think Dr. O'Fallon was next and then we'll do Dr. Gorman, Dr. Bier, Dr. Moore, and then we'll have to move on because we're almost an hour beyond.

DR. GRYLACK: I stuck to my 10 minutes.

CHAIR CHESNEY: It says Cardio-Renal people.

DR. O'FALLON: Here's the deal. The

question that we were asked when we walked in here was have we got enough information now that we can tell the FDA to stop this extra special monitoring. This one, esmolol, and there's another one down here, raise a real question in my mind how much information do we even have. How many patients, kids, were treated with the stuff during the year.

I mean, these reports are coming in, you know, passively. We have only, what, two, I think. No, there's only one in this year. How many were treated? I think what we're doing, Dianne, is not -- when we're dealing with this thing we're trying to estimate serious event rates and identify some of the rarer things that the kids have, the adverse events that afflict kids are. If we've only seen 50 or 100 or 150, we have small chances of picking up some of the rarer that could be killing events.

DR. GRYLACK: Well, we know certainly in the case of esmolol how many patients were in the studies and we can collect that information prospectively. However, with the patients who weren't in the studies there were 150 or 160 patients based on

the databases that we have. As was pointed out, it is passive reporting so we don't truly know perhaps how many of those 160 during the post-exclusivity period had --

DR. O'FALLON: How many were treated? That's the big thing.

CHAIR CHESNEY: That's why I want us to move ahead because I think that's the bigger picture and we can't get to that until we get through these drugs so, Dr. Gorman.

DR. GORMAN: In 1994 I think there was a position put in the label for the pediatric information and I would think that as we move forward a reasonable suggestion might be that if a drug obtains marketing exclusivity, that at least it says in that section, "Pediatric marketing exclusivity has been granted based on X number of studies with X number of patients. For further details see _____."

I don't think that's up for any debate in the sense that it's all factual and I know how the FDA wants their labels to be factual and accurate and that would allow them to be factual and accurate and then

put all the wordsmithing and spin-doctoring and obfuscation in the reports from other people.

DR. MURPHY: You're very close to what was in John's e-mail.

CHAIR CHESNEY: Thank you. I think we've gotten that issue down cold now.

Dr. Bier.

DR. BIER: Well, I guess I'm still back to the power issue. We're talking about events that are consistent with the adult events or consistent with the label, etc. Do we have the power to tell what's inconsistent? We don't have in this number of individuals the power to tell anything is inconsistent with those.

CHAIR CHESNEY: We don't and that's the bigger picture also that we're going to be talking about in a few minutes.

Dr. Moore.

DR. MOORE: I guess I have a similar comment. It strikes me that what we're trying to discern here in terms of these passive reports is whether or not the pediatric passive reporting that we

have sort of focused on over the past year is in any way different from the reports that we're getting from the much larger group of adult patients.

I'm just a little bit confused. Are we talking about labels here? We're getting diverted in terms of the question that we're supposed to address here. We're really just talking about whether we want to focus on pediatric reporting or not.

It seems to me that the labeling is an additional issue to that. I think that in terms of the reports that have been received about, I'll pick esmolol here, they are not particularly alarming in the sense that they are not particularly different from the background reporting on the adult patient group.

CHAIR CHESNEY: I think what we're being asked is there was one pediatric report in the post-exclusivity period which was in a teenager in whom the drug was actually contraindicated. The label says not to use it in somebody who is vasoconstricted because of a lower body temperature. I think you made that point.

So the only adverse event at all that had to do with children that was reported through the air system in this year was this one patient. We're being asked as to whether we can accept that as comforting enough that the FDA no longer has to just focus on the pediatric age group or if we feel like they should continue to do this for at least another year and then come back to us with another report.

Can I see a show of hands as to those who feel that they need to continue to actively look at all the pediatric cases reported for the next year or the second year after exclusivity for esmolol. How many people would support that? Eight support. Who doesn't? Four to do not support it so I guess we are looking at reviewing this again in another year.

DR. MURPHY: Joan, I have one question.

CHAIR CHESNEY: Yes.

DR. MURPHY: Okay. Now, people keep saying, "We don't know how often it was used." We are giving you how many prescriptions in the use data. What else do you -- we don't need to -- I think we get to the safety discussion this afternoon. Would you

please give us some more detailed input on that because we spend a lot of time and we pay for a lot of databases to try to get pediatric use and this is the use data we have. If it's not providing what you need, we need to hear from you how it's not providing what you need.

CHAIR CHESNEY: I think we all have concerns about matching what you give us with the adverse events so we'll do that in the bigger picture time.

Our next speaker is Dr. -- thank you, Dr. Grylack for more than usual rigorous --

DR. GRYLACK: It was a pleasure. I didn't develop any orthostatic hypotension.

CHAIR CHESNEY: Are you orthostatic because you're cold?

DR. GRYLACK: Right.

CHAIR CHESNEY: Dianne, I don't have any introduction for Dr. Sachs.

DR. GRYLACK: I have it.

CHAIR CHESNEY: Oh, you do. I'm sorry. Thank you.

DR. GRYLACK: It's my pleasure to introduce Dr. Hari Sachs, pediatric medical officer, professor of pediatrics at George Washington University and a practicing pediatrician.

DR. SACHS: Thank you for that kind introduction. I hope you guys have a heart, okay? It's Valentine's Day. I will be talking about two drugs that are related to obesity management, orlistat and glyburide-metformin.

I do want to say before starting this orlistat presentation that the last slide, the conclusion slide, that went out on the web, has an error. Hopefully the presentation will include the updated slide.

Orlistat, or trade name Xenical, is a lipase inhibitor marketed by Roche and it was approved originally in April 1999 and granted pediatric exclusivity in September 2003. Orlistat acts by inhibiting dietary absorption of fat which is important in its adverse event profile.

Orlistat is indicated for adolescents and adults over 12 in conjunction with weight loss for

obesity management. The decision to treat the patient is based on body mass index over 30 or lower body mass index along with risk factors such as hypertension, diabetes or dyslipidemia. The recommended dosage is the same for adults and adolescents.

Prescriptions for orlistat have been decreasing in both adult and pediatric patients and this is primary outpatient data. Prescriptions in females tend to outnumber those in males by a ratio of three to one, a trend that is observed in children as well. Orlistat is prescribed primarily in adults with pediatrics accounting for less than 1 percent of prescriptions and I believe the total is about 4,000.

The top prescribers, not surprisingly, were internists, family practitioners, and osteopaths and, once again, pediatricians like myself accounted for a very small amount of these prescriptions. The most common diagnosis is obesity in adults but because of sparse data we can't determine that for kids.

I wanted to highlight here is the website where you can find these reviews and we'll look at the studies that were performed that resulted in

exclusivity. There was a pharmacodynamic study that looked at the effect of orlistat on mineral balance as well as its safety and efficacy. Nested within the study was population pharmacokinetics.

The pharmacodynamic assessments that were performed occurred in a three-week inpatient trial of 32 adolescents. They all were placed on a reduced calorie diet along with the drug and multi-vitamin supplementation. Selected minerals, electrolytes, and measures of kidney function were determined periodically. Fecal fat content was determined daily. Glad I wasn't there.

Compared with placebo orlistat did not affect the majority of the minerals but it did significantly increase fecal fat excretion and decreased iron balance and 94 percent of participants completed this study.

The efficacy study was a much longer trial of 539 obese adolescents. Obesity was defined as a body mass index greater than 97 percent for age and gender. The primary efficacy end point was a change in body mass index to allow for growth.

Secondary efficacy endpoints included change in body weight, cholesterol, blood pressure, glucose tolerance and insulin levels.

As you can see, this study also monitored a large number of safety parameters over the year including growth, pubertal development, gastrointestinal symptoms, fat absorption, body composition, EKG changes, liver and gallbladder.

It was a year-long study so 65 percent completed it but compared with placebo orlistat did have a modest clinical benefit and significantly decreased body mass index and waist and hip circumference as well as the proportion of patients that achieved a five or 10 percent reduction in body mass index. In fact, it was almost double of the placebo. There are similar improvements in the weight percent as well.

From a safety point of view orlistat treatment did not significantly impact blood pressure or levels of lipids or glucose intolerance. In this subgroup that had DEXA body composition determination the weight loss did appear to be due to a decrease in

fat and not in muscle mass.

Not unexpectedly, though, there was an increase of fatty and oily stools and decreased absorption of fat-soluble vitamins in the treating group. These finding were similar to those seen in adults. Consequently, there is a precaution in the label to administer the drug with a multi-vitamin that contains fat-soluble vitamins and beta-carotene.

The clinical trial is described at length in the pediatric use section and a statement that the adverse event profile in adolescents is similar to that in adults appears in the label.

Now I'll describe some other labeling that is important for the adverse events that will be discussed, although there really aren't many pediatric ones, and for pediatrics in general. Orlistat is contraindicated in patients who have known cholestasis or malabsorption. If dietary fat content is high, then you expect a bunch of gastrointestinal symptoms. The potential misuse for patients with anorexia is also described.

Orlistat is considered a pregnancy

category B drug because animal studies have shown a potential for hydrocephalus at high doses but there's not really a study in humans. Gastrointestinal adverse events, as I said, are very common.

Now looking at the adverse events, since drug approval in 1999 through October of 2004 less than 1 percent of the reports have been pediatric which roughly parallels the use. And, again, note that these reports include duplicates and their raw counts.

This is kind of a gross way, and I forgive the word, of looking at the reports in a gamish. It's the top 20 most commonly reported events in adults that might include some duplicates. They are described. When we mention whether it's labeled or unlabeled, we are basically referring to the term that's used in the adverse event report, in the MedRA database whether that term is actually found in the label.

But if you look closely, many of the "unlabeled" terms are really related to labeled terms or they are actually labeled. A lot of the events

actually really describe gastrointestinal events or malabsorption or perhaps headache.

And these are the pediatric adverse events. Many of these are not actually specifically labeled because they relate to neonatal disorders or accidental exposures. There is one case, cholelithiasis, which was a serious adverse event that was reported during the clinical trial and the patient did require hospitalization and surgery. But, again, I want you to note that known cholelithiasis is a contraindication to use.

In the one-year post-exclusivity there's only one pediatric adverse event which I'll discuss shortly. In the adults the top 20 are listed here. Once again, most of them are labeled or related to unlabeled events. But we do see cholelithiasis and gallstone pancreatitis which I want to mention is associated both with increased body mass index. In other words, the underlying disease, and may be associated with weight loss or it could be the therapy.

The pediatric adverse event involves a

neonate who was delivered by C-section who was noted to have unstable hips, a fact that was not confirmed on follow-up. The mother did receive therapy during her first trimester. She was a smoker and had a contraceptive implant that was removed five months prior to the pregnancy.

So, in summary, there's really very few adverse events and there's minimal use so I'm not sure that we can draw some meaningful conclusions but there were reports of cholelithiasis during the trials and in post-market surveillance. We don't know what the relationship between drug treatment or the rapid weight loss and perhaps the obesity to begin with is. Our thinking was that we would recommend continued monitoring of this product if you all concur. Are there any questions?

CHAIR CHESNEY: I think our agenda calls for you to go ahead and do the second one and then we'll --

DR. SACHS: Then you'll hit me.

CHAIR CHESNEY: -- give you both.

DR. SACHS: Once again I want to acknowledge all the folks from the Office of Drug Safety, the Division of Metabolic and Endocrine Drug Products and the Office of Regulatory Policy who have contributed to these.

Now let's talk about glyburide-metformin. Glyburide-metformin, or trade name Glucovance, is a combination antihyperglycemic agent which is marketed by Bristol-Myers Squibb. Glucovance is an adjunct treatment for Type 2 diabetes along with appropriate diet and exercise and a second line therapy in patients whose primary treatment with metformin or sulfonylurea have failed.

It was approved originally in July 2000 and pediatric exclusivity was granted in October 2003. The dose of this combination product is the same in adults and adolescence and each component of the combination adds to the efficacy of the product, in this case glyburide by stimulating the release of insulin, augments, metformins, and crude glucose tolerance.

Once again, since the use of glyburide-

metformin is primarily in outpatients, the usage was not determined in inpatients and while oral antihyperglycemic prescriptions in general have been increasing, Glucovance has accounted for a large proportion of the combination product market share. It's over 6.8 million prescriptions. In contrast, though, the use in pediatrics is relatively minimal, less than 0.06 percent.

Not surprisingly internists and family practitioners write the majority of prescriptions for this agent and pediatricians write very few. The most common indication in adults is diabetes without complications and there is insufficient data available to allow us to state what it was in kids.

Once again, we're going to look at the studies that were performed for exclusivity. There were two studies that were performed in pediatric patients with Type 2 diabetes in response to a written request, PK and the efficacy and safety study.

The pharmacokinetics study was a single dose PK study of glyburide-metformin and it found that pharmacokinetics were pretty much compatible between

children and adolescents and did not differ significantly from adults. There was no apparent relationship between body surface area on dose based on the limited data.

To demonstrate efficacy and safety there was a 26-week trial of 167 adolescents with Type 2 diabetes. These patients were over 50 percentile for weight and did not have adequate glycemic control based on diet or exercise or perhaps with a single drug.

Inadequate glycemic control was defined as a hemoglobin A1c greater than 6.4 percent and a mean fasting glucose greater than 200 but less than 350. The primary efficacy outcome in this trial was the decrease in hemoglobin A1c. But unlike the findings in the adult population, the combination product was not superior to monotherapy.

One reason for this might be that in the adult trial the superiority of Glucovance was primarily noted in patients who had average hemoglobin A1cs over 9 percent or were treatment naive. In the pediatric trial the average hemoglobin A1c was about

7.8 and almost half the patients were not treatment naive.

Gastrointestinal intolerance, once again, is expected and hypoglycemia with the combination. During the trial no patient experienced a serious adverse event, had a marked laboratory abnormality or discontinued the trial prematurely due to an adverse event. Thus, there are no unexpected safety findings.

What was noted was perhaps because the doses of metformin and the combination are lower than what is used in monotherapy. There was really less GI complaints from the combination product but if hypoglycemia did occur, it seemed to be related to the dose of the glyburide.

So the label was changed as follows. The clinical trial is described in the pediatric use section and then the statement is made that Glucovance is not shown to be statistically superior to either metformin or glyburide alone with respect to reducing hemoglobin A1c. But the statement "Glucovance is not recommended for pediatric patients" was removed from the label.

Now, I'm going to look a little bit at the labeling so you have a context for the adverse events and just some general pediatric important stuff. It's a pregnancy category B drug based on animal studies which suggest that hypoglycemia is associated with congenital malformations. The combination is contraindicated in the face of renal disfunction, congestive heart failure, and acute metabolic acidosis.

There is a box warning regarding lactic acidosis which relates mostly to the metformin component. There's a special warning about the potential for increased cardiovascular mortality compared to dietary management with or without insulin. That may be more relevant for older adults but, nonetheless, it is a special warning.

Since the drug approval through November 2004 there have been no pediatric adverse event reports reported for glyburide-metformin. There have been no pediatric reports during the exclusivity period. This list the top 20 most common event reports in the adults in the post-exclusivity period.

Most of the adverse events, once again, do appear to be related to labeled events.

You guys may think differently but due to the fact that it's not used much in children and there are not very many reports, we thought this would complete the adverse event reporting for the drug and would not recommend special monitoring but would want it to return to routine monitoring. But we're interested in your concurrence and if you have any questions. Once again, I do want to thank all these folks that were involved.

CHAIR CHESNEY: Thank you, Dr. Sachs. Let's take the easiest route first and talk about Glucovance. Does anybody have specific questions about Glucovance in particular with respect to the recommendation to return to regular AERS monitoring? No questions. Does anybody disagree with the recommendation to return to routine AERS monitoring? Thank you.

Now, questions for Xenical. The recommendation here is that they continue to actively monitor all pediatric adverse event reports for

another year, for two years post-exclusivity and to bring it back to the committee. Any questions? Anybody not agree with that recommendation?

DR. SACHS: For Glucovance we'd like it to return to the routine monitoring but for orlistat we actually would like to continue monitoring it.

CHAIR CHESNEY: I think I asked if anybody disagreed with the recommendation on Glucovance which was to return to routine monitoring and nobody put up their hand.

DR. O'FALLON: It's okay with me, you know. If you think this is simply never used in kids essentially, very, very rarely used in kids, then the fact that we have almost no information about it probably doesn't matter. But if we really think that it's going to be used in kids, then we don't have very much information about it. I'm not a medical doctor. I'm just a statistician but, you know, how you cut your data makes a difference to me.

DR. SACHS: It's truly hard to know if we monitor it for another year if there's been no reports and there's minimal use that there will be anymore

reports or anymore use. It really depends on how you look on this one.

DR. MURPHY: And also it tells you that we looked at it and we don't see any benefit from the combination product. We're hoping there will be little use. It doesn't mean that but, I mean, we're saying right now we don't have a valid reason to go forward to say we should focus on this. Considering the limited resources you've got to try to focus on the ones that you think might yield something.

CHAIR CHESNEY: You've actually had no reports since July of 2000.

DR. MURPHY: Right, in peds.

CHAIR CHESNEY: Does anybody disagree with the recommendation to return to routine AERS monitoring for Glucovance? Dr. Bier.

DR. BIER: I'm not sure I disagree with it but I'm having a problem with our consistency or, at least, my consistency on this. If there's no information for the first two drugs, I mean, how come there's no information for Glucovance? I would say that we really don't know whether the use is going to

increase or decrease. With the increasing prevalence of adolescent obesity, I think there's a major thrust among pediatric endocrinologists to start considering the use of these drugs. I would argue that the use is likely to go up.

DR. MURPHY: The combination product. You think the combination product will go up?

DR. BIER: That's hard to answer I think. It's more likely to be a single drug.

DR. MURPHY: Right.

DR. SACHS: And, remember, it still gets monitored. It's just whether or not we really go through it like this and formally report.

CHAIR CHESNEY: Dr. Moore.

DR. MOORE: If you just look at the data that's provided here there is something on the order of 7 million prescriptions written and .6 percent of them or so are pediatrics. That means there are 42,000 or so prescriptions for this drug in the pediatric population. Given that as a background, there are no events reported. I mean, I don't think we're entirely working with no data here. Minimal use

is -- this is probably being used a lot more than the first two drugs we discussed.

DR. MURPHY: And it has new labeling which is not encouraging so I guess that's what we're saying. We do have some information. We don't see anything -- we have new labeling that says we don't see any benefit of this combination. We just feel that this is not the area to focus on.

CHAIR CHESNEY: Okay. Let me just ask one more time does anybody not agree with the agency's recommendation for Glucovance? Okay. So we agree with that. Now we will return to Xenical. Here the agency is recommending that there be continued focus on pediatric, continued attention to all pediatric case reports for another year to bring it to two years post-exclusivity and then report back to the committee.

Does anybody feel that is not warranted, that they could return to their routine AERS reporting? And are there any questions about Xenical? About the presentation. Okay. So just one more time, nobody disagrees -- is there anybody who

disagrees with the agency's recommendation for Xenical?

DR. SACHS: Thank you all very much.

CHAIR CHESNEY: We're just debating here whether to take a break at this point and then hear the next two reports and move into the other session. Does anybody have any strong feelings about that? We don't have anybody scheduled for the open public hearing which might mean we have to go a little bit longer. All right. Why don't we take a break for 10 minutes and be back here at 4:00. Thank you.

(Whereupon, at 3:52 p.m. off the record until 4:03 p.m.)

CHAIR CHESNEY: If I can just ask. Nobody has signed up for the open public hearing. Is there anybody that would like to make any comments who has not signed up? All right. Thank you. We're going to change the format for the next two talks slightly in that we'll have questions and answers for the atovaquone-proguanil presentation right after the presentation because somebody who may want to comment does have to leave early. If Dr. Shapiro is here, we

can proceed with the next drug.

DR. IYASU: I'll just briefly introduce Dr. Shapiro. He's a pediatric infectious disease specialist with a Ph.D. in biochemistry. His past research includes work in immunology, infectious disease and molecular pharmacology. He's also had training in pediatric nephrology and medical genetics. Dr. Shapiro has been with the Division of Pediatric Drug Development for over a year working as a medical officer.

DR. SHAPIRO: Thank you, Solomon. I would like to continue on with talking about the adverse events for atovaquone-proguanil. Atovaquone-proguanil comes in two different formulations, Malarone and Malarone Pediatric. Malarone is approved for the treatment and prophylaxis of plasmodium falciparum malaria. It was originally approved in July of 2000. The sponsor was granted pediatric exclusivity in August of 2003.

Now to go on to the drug use trends. Malarone accounted for a little more than 5 percent of the approximately 3.7 million prescriptions dispensed

for anti-malarials in the year following the granting of exclusivity. Dispensed prescriptions for Malarone Pediatric increased 34.5 percent during the time after the granting of exclusivity compared to the year prior. Pediatricians were responsible for approximately 40 percent of the Malarone Pediatric prescriptions.

Now, going on to the pediatric exclusivity studies, I would like to describe the three different trials. The first trial was a treatment trial involving 200 patients which compared the safety and efficacy of atovaquone-proguanil to amodiaquine and the treatment of acute uncomplicated plasmodium falciparum malaria in patients weighing 5 to 11 kilograms.

The results of this trial were that there was an adequate clinical response obtained in 95 percent of the patients treated with atovaquone-proguanil versus 53 of the patients who were treated with amodiaquine. I need to mention that in the U.S. there are other comparatives that could have been used in addition to amodiaquine.

The second trial was a malaria prophylaxis trial consisting of 330 patients. This was a double-blind placebo-controlled study evaluating the safety and efficacy of atovaquone-proguanil in the prevention of plasmodium falciparum malaria in an endemic area in pediatric patients weighing 11 to 40 kilos.

The method works like this. These patients were diagnosed with plasmodium falciparum malaria. They were treated with artesunate and then following artesunate therapy, then they were randomized to atovaquone-proguanil or a placebo.

Now, the results of this trial was that less than 1 percent of the patients treated with atovaquone-proguanil for prophylaxis had a treatment failure as compared to 22 percent of the untreated patients.

The third trial with another malaria prophylaxis trial involving 221 patients, this was an international open-label randomized trial to compare atovaquone-proguanil to chloroquine-proguanil in the prevention of malaria and nonimmune pediatric patients weighing 11 to 50 kilograms fell into an endemic area.

One thing to note that in the results of the study there were no malaria cases in either arm of the study and the study was not large enough. Therefore, we could not make statements of comparative efficacy.

Now, labeling that resulted from these exclusivity studies was, first, the inclusion of pharmacokinetic clearance data as a function of body weight for patients weighing 11 kilos and greater. It also extended labeling of atovaquone-proguanil down to 5 kilograms for the treatment of acute uncomplicated P. falciparum malaria and added additional safety data for these patients.

Also, relevant safety data that resulted from this was that the most commonly reported adverse events attributable to atovaquone-proguanil for the treatment of malaria was diarrhea in patients 5 to less than 11 kilograms, and vomiting and pruritis for patients 11 to 40 kilograms.

In the prophylaxis trial the most commonly reported adverse event attributable either to atovaquone-proguanil placebo was headache, fever, and

abdominal pain. In other prophylaxis trials treatment-emergent events included abdominal pain and vomiting, headache and cough.

Now, one thing to do we always look at post-marketing to see if things come up in the way to look at safety and one of them was for cutaneous reactions including rash and photosensitivity and urticaria were reported. Also there was rare cases of erythema multiform and Stevens-Johnson syndrome. In the central nervous system one thing we do take a note of is that there were rare cases of seizures and psychotic events such as hallucinations but the causal relationship has not been established.

As part of our adverse report, as you know, we take two periods, the period since marketing approval and look at it for atovaquone-proguanil. The total number of reports for all ages was 293 reports of which 240 were serious and included six deaths. In the pediatric reports there were 17 reports of adverse events of which 15 were serious and there was two unduplicated reports of patient death.

Now, to go on to the pediatric deaths that

were reported prior to post-exclusivity period. I should note that both of these deaths occurred while on treatment for plasmodium falciparum malaria. The first patient with a 14-month-old was severe anemia, three days of presumed fever, and hepatosplenomegaly.

The patient was treated with chloroquine and paracetamol for two days, had a moderate parasite count and hematocrit of 12 percent. This patient subsequently received two days of atovaquone-proguanil and became dyspneic with increasing anemia and severe hypoglycemia.

The patient was placed on oxygen and died before receiving a blood transfusion. This death was presumed to be due to severe malarial anemia and hypoglycemia but a causal link to atovaquone-proguanil could not be excluded.

Now, on the second patient also occurred prior to the post-exclusivity period with a 22-month-old with severe anemia, five days of presumed fever, anorexia, occasional vomiting, and tachycardia. That patient was treated with chloroquine and paracetamol for three days, had a moderate parasite count and

hematocrit of 14 percent.

This patient received one dose of atovaquone-proguanil and subsequently this patient deteriorated and died 45 minutes after that dose. This death was presumed to be due to severe malarial anemia but a causal link to atovaquone-proguanil could not be excluded.

Now, going to the adverse events during the one-year post-exclusivity period. This is, again, reports for all ages. There was 122 reports of which 89 were serious and there were no deaths. The pediatric reports were seven adverse event reports of which six were serious and there were no deaths.

Now, we did summarize here the top 10 reported adult adverse events during the one-year post-exclusivity period which are listed below. The ones that are underlined are the ones that are not described in the label.

Now, to go onto the pediatric adverse events during the one-year post-exclusivity period, actually there were five unduplicated pediatric reports of patients on atovaquone-proguanil for

malaria prophylaxis. The first four cases here are allergic type of reactions which included facial edema, blepharitis, pruritis urticaria, and acute psoriaform reaction. I should also mention that the patient with acute psoriaform reaction had increased transaminase.

Now, let's go on to the fifth case. This is a 16-year-old who was on atovaquone-proguanil for 19 days for malaria prophylaxis. One to two days after completing the prophylaxis the patient woke up with blurry vision and was unable to see three inches. This patient saw the primary medical doctor, an ophthalmologist, and a retinal specialist and was given prescription glasses. But this case was reported by a nonhealth professional who described the patient as being "legally blind."

The ophthalmologist diagnosed them with acute myopia, possibly a drug effect. The retinal specialist noted retinal striae in both eyes. I should mention that the acute myopia resolved after one week with this patient.

Now, to summarize for the pediatric

adverse events in the way of eye disorders, current labeling for atovaquone-proguanil derived from the results of the adult malaria prophylaxis trial lists visual difficulties in 2 percent of the patients on atovaquone-proguanil versus 3 percent of the patients on amodiaquine.

Since marketing approval there have been post-marketing adverse event reports of adults with visual blurring, eye pain, eye swelling, and eye disorders. Hypersensitivity including cutaneous reactions have been addressed in current labeling. Elevation of transaminase associated with the treatment of malaria have also been described in current labeling.

Now, summary. This completed a one-year post-exclusivity adverse event monitoring as mandated by the Best Pharmaceuticals for Children Act. The Office of Pediatric Therapeutics recommends that this drug return to FDA's routine monitoring of adverse events. We ask that you, the Advisory Committee, do concur with this recommendation.

I would like to acknowledge the members of

the Office of Drug Safety, the Division of Special Pathogens and Immune Drug Products, and the Office of Regulatory Policy for their assistance and their work in helping me develop this presentation.

CHAIR CHESNEY: Thank you, Dr. Shapiro. I'm always glad when people within the FDA don't know what all these initials stand for. It seems overwhelming to those of us on the outside.

Any questions for Dr. Shapiro about this drug for treatment of prophylaxis of malaria? No questions. Is there anybody on the committee who disagrees with the FDA's recommendation for this drug which would be to return to routine nonpediatric focused AERS reporting? Nobody disagrees? My goodness. Thank you.

We'll go on to your next drug.

DR. SHAPIRO: Okay. Great. Going on to nelfinavir, please. I would like to describe the adverse events for nelfinavir mesylate. Nelfinavir, also known as Viracept, is an HIV protease inhibitor which was approved in 1997. The indication is for the treatment of HIV infection for patients two years and

older. The sponsor was granted pediatric exclusivity in September of 2003.

Now, to go on to drug trends in out-patient setting, nelfinavir accounted for approximately 16 percent of the 1.9 million prescriptions for HIV protease inhibitors prescribed in the U.S. during the period after exclusivity was granted.

Dispensed prescriptions for nelfinavir decreased approximately 22 percent during the year after exclusivity was granted as compared to the year prior. Pediatricians were responsible for only 3 percent of the prescriptions of nelfinavir dispensed in the U.S. during the period after the granting of exclusivity.

Now, to go on to the pediatric exclusivity studies for nelfinavir. There were five trials and greater than 400 HIV-infected patients from birth to 17 years of age after examining pharmacokinetics safety and activity of nelfinavir mesylate.

One thing I should note is one thing that complicated the trial was the highly variable drug

exposure which was concerned because this was considered to be secondary to difficulties due to adherence and the problem with adequate food intake in this population. I should note that this drug must be taken with food to allow for proper absorption.

The response rate in children less than two years of age appeared to be less than that of patients two years and older in some of the studies. This led to revised dosing recommendation for pediatric patients two years and older and it was not recommended to be used for patients younger than two years.

Labeling changes that resulted from these exclusivity studies included inclusion of pharmacokinetic data for pediatric patients one week to 13 years of age demonstrating this variable drug exposure. For children two years and older the dosing changed from 20 to 30 milligrams three times a day to 25 to 35 milligrams per kilo three times a day or 45 to 55 milligrams per kilo twice a day and a modified dosing chart was added to the label. Also, the safety data base was expanded from 38 patients to

approximately 400 and the label listed the most common pediatric adverse events.

Now, to go on to relevant safety labeling. The most common reported treatment of emerging adverse events with the treatment of nelfinavir were diarrhea, leukopenia/neutropenia rash, anorexia, and abdominal pain. Diarrhea regardless of the relationship to the study drug was reported in 39 to 47 percent of pediatric patients receiving nelfinavir in two of the larger pediatric treatment trials.

Leukopenia/ neutropenia was the laboratory abnormality that was most commonly reported as a significant event across the pediatric studies.

Going on to the adverse event reports dealing with the period after market approval. This is for all ages. There was approximately 3,300 reports of adverse events of which 3,200 were serious and there were 417 deaths. Pediatric reports had 377 adverse event reports in which 374 were serious and there were 19 deaths.

Now, in the post-exclusivity period total number of reports for all ages, there were 269 reports

of adverse events of which 264 were serious and there were 33 deaths. Going on to the pediatric reports, there were 30 reports, all were serious, and this included two patient deaths.

Now, the most commonly reported adult adverse events during this one-year post-exclusivity period are listed below. The underlying adverse events are not described in nelfinavir's label.

Now, going on and discussing the pediatric adverse events for nelfinavir we need to distinguish two types of exposures. First is direct exposure. These are patients with either suspected or actual HIV who are being treated with anti-retrovirals. One thing is that nelfinavir is used in combination with other anti-retrovirals so it's very hard to attribute causality to the adverse events. The second type of exposure is indirect. This is occurs in-utero during pregnancy for HIV positive moms who are on anti-retroviral therapy.

As you know, the exposed infants may or may not be HIV infected and that most newborns receive anti-retroviral prophylaxis following delivery. This

may complicate the interpretation of adverse events associated with in-utero exposure. I also wanted to mention that there has been a possible association with combination anti-retroviral therapy and premature delivery.

Now, the pediatric adverse events now dealing with direct exposure during the one-year post-exclusivity period. This includes three patients with all these adverse events listed below. As you can see, most of them are unlabeled and they are underlined because they are not described in nelfinavir's label.

I would like to discuss one of the adverse events which was a pediatric death in a directly exposed patient. This was a 60-week old HIV positive toddler who was an ex-30 week preemie who had been on open-label trial consisting of stavudine, didanosine and nelfinavir.

This patient had two episodes each -- at least two episodes each of bronchiolitis and suspected arthritis. This patient died secondary to respiratory distress due to bronchiolitis obliterans when being

hospitalized for suspected arthritis.

Now, going on to pediatric adverse events from the other type of exposure which is in-utero exposure during the post-exclusivity period. The most common reported adverse events were prematurity, birth by C-section, metabolic derangements, gastroesophageal reflux disease, and patent ductus arteriosus.

One thing I want to get back is we talked before about prematurity. There's a possible association with combination anti-retroviral therapy but also these moms are not well. Many of them are sick and any mother with chronic disease has a higher incident of premature delivery.

Also, C-section delivery is used most commonly as a means to try to minimize the risk of HIV transmission and increased latex acid is seen on those patients who are on nucleoside reverse transcriptase inhibitors which could either be the mom or the patient itself.

I want to also discuss the one pediatric death that was associated with in-utero exposure. This is a term infant born to a mother who discovered

her HIV positive status in the third trimester. The mother was started on zidovudine, lamivudine, and nelfinavir two weeks prior to delivery. This baby was delivered by C-section with an Apgar of 10.

The infant received two does of zidovudine post-pardum and was found dead at 20 hours of life. Radiographic studies, cerebral spinal fluid cultures and electrolyte labs were normal. Blood lactate level was slightly elevated and anemia was also noted. This patient's HIV/PCR of the blood was negative. The autopsy was consistent with asphyxia and the relationship to drug exposure is unclear with this patient.

Now, to summarize the safety information for nelfinavir. No consistent safety signal has been identified in the three reported pediatric adverse event cases. These are the ones due to direct exposure. Prematurity was the most common adverse event observed in infants with in-utero exposure and, as has been discussed, has been reportedly associated with combination anti-retroviral therapy during pregnancy.

This completes the one-year post-exclusivity adverse event monitoring as mandated by the Best Pharmaceutical for Children Act. FDA recommends routine monitoring of adverse events for this drug in all populations. Does the Advisory Committee concur?

I would like to acknowledge the following listed individuals whose work helped in the preparation for this presentation. Thank you.

CHAIR CHESNEY: Thank you, Dr. Shapiro. I have one question. In your last slide no consistent safety signal identified in the three reported pediatric adverse event cases. But on slide eight it has 30 serious and two deaths. Which were the three that you were referring to in your last slide?

DR. SHAPIRO: Okay. These reports include both the direct and indirect exposure. You have the three direct exposures and then you have the 24 so they make up the 27 unduplicated reports.

CHAIR CHESNEY: So the three in your summary slide are direct.

DR. SHAPIRO: Direct.

CHAIR CHESNEY: And the 27 are indirect.

DR. SHAPIRO: No. There were 27 unduplicated reports.

CHAIR CHESNEY: Oh, I see. Yes.

DR. SHAPIRO: Three were the direct exposure and 24 were the in-utero exposure.

CHAIR CHESNEY: Thank you.

Other questions for Dr. Shapiro?

DR. MURPHY: We don't want to keep the numbers the same so you might get it unconfused.

CHAIR CHESNEY: Thank you for that. No other questions and your recommendation is that this be returned to routine monitoring.

DR. SHAPIRO: Correct.

CHAIR CHESNEY: Does anybody on the committee disagree with returning to routine monitoring for this drug?

DR. SANTANA: Can I ask a question before we answer that? I'm sorry, John. The issue of the decreasing prescriptions is that because this drug is now one of those that's included in these new pills that have two or three drugs and, therefore, the

actual usage of the drug is still high but the individual prescription for the individual drug is low?

DR. SHAPIRO: I think we're only looking at -- nelfinavir is just one of the protease inhibitors and there are other protease inhibitors that have come on-line that people are using more commonly. Also people are going to protease-bearing regimes like the non-nucleoside reverse transcriptase inhibitors which some people want to save the protease for later because they are worried about resistance.

DR. SANTANA: So you think this decrease is real then?

DR. SHAPIRO: Yes.

CHAIR CHESNEY: I think you have a consensus to go along with your recommendation.

DR. SHAPIRO: Okay. Thank you.

CHAIR CHESNEY: Thank you very much. Now I think we turn to the heart of the matter. Dr. Iyasu is going to start us off.

DR. IYASU: Okay. I know you've had a very busy day and I'll try to go through this quickly

but with some detail. We want to ask you for some advice on a very important topic. You have already raised some of those questions that we are concerned about. I want to give you a little background.

You've heard this before but this mandated report which is post-exclusivity for one year is under BPCA. There is a specific section for it. And there is a rationale that we think is a basis for this. Exclusivity is granted to a drug and you must know that it's not based on approved indication.

It's just that they have done the studies so the thinking is that once approved and there is an indication there will be a potential for increased use in the pediatric population and, therefore, there might be more post-marketing reports related to this.

The mandate also says that we have to report a summary of our review for one year to the pediatric Advisory Committee. The committee kind of advise us as to what to do with the reports. I want to give you a little history of how we came from the enactment of this law in 2002 January.

We developed an internal process. This

includes really not just the pediatric group but this is really a CDER activity which includes also the Commissioner's Office now, which is OPT. We developed an internal process and template for the review process where the Office of Drug Safety, which is within CDER, does the detailed evaluation of the drug use in the pediatric population and produces a report.

The same office but a different division within the same Office of Drug Safety reviews the adverse event reports for the one year period. They try to look at it from the perspective of pediatrics but also are in a position to evaluate what is reported in adults.

The Division of Pediatric Drug Development, which is working with the Office of Pediatric Therapeutics under which this activity really falls, prepares the background materials for these meetings, evaluate and synthesize all the different pieces of information regarding a particular drug which includes the adverse event reviews, clinical pharmacology and tox reviews, and also the literature if there are any reports of safety

literature for this particular drug, and then puts together this presentation for the public discussion.

Over the last two years we have made some enhancements to what we actually report to you from just slide presentations that we used to do on the adverse events. Now we have been including the primary reviews that you get instead of the secondary reviews so you have more information about each of the drugs, the use information and the detailed analysis that is produced by the Office of Drug Safety.

We provide you also in your package written summary of the clinical and pharmacology and toxicology review of the exclusivity studies so you have some background about where the genesis is for this drug. Then the slide presentations that I have prepared for you and for the public presentation.

We've also improved the timeline for providing the information. We give you the background materials ahead of time now. We also provide the same to the sponsors in terms of the slide presentation. We try to give them 72 hours ahead of time.

So far this is our 6th pediatric Advisory Committee meeting plus the precursor which is the subcommittee. From 2003 to 2005 we've had 34 drugs now presented for public discussion. There have been important discussions pertaining to several areas here.

You will recall that there was a discussion of neonatal withdrawal syndrome, toxicity associated with maternal exposures to SSRIs and you gave us some very good advice regarding that.

Suicidal behavior from anti-depressant medications and you've had two meetings on this subject.

Although the detection of the signals for suicidality were not coming primarily from post-marketing adverse event reports, the emergence of those and the reporting of those events in the post-marketing arena did accelerate the timeline for review of the clinical trials and they were important in focusing the discussion about what might be the potential risks with exposure to these drugs.

We've had a discussion about pediatric

deaths from inappropriate use of fentanyl transdermal patch and you gave us very good advice on this. There has been new labeling added to address issues you discussed about the appropriate use of this medication, the definitions about what we mean by opiate tolerant patients, what situation and what dosing to give.

There is also a risk minimization plan initiated. There has been, I think, very good safety information that has been generated from this limited review. There's a lot more that we can do but getting at least some information has been helpful from this review process. I know I understand their frustration. We are as frustrated as you are with the limitations of data.

A few months ago we asked you for feedback about the BPCA-mandated post-marketing adverse event reporting: What are the areas that we need to improve on? What kind of information would you like to see: Were the format and the presentations useful in helping you assess a particular safety risk in pediatrics?

And you gave us some very good feedback. Some of them very challenging. Some of them easy to fix but a lot of them aren't and many of the questions that you are raising today as well. I grouped them into four areas and one big area is about measuring exposure. How many pediatric patients are treated and how many are exposed during a particular year. That is a very big issue.

The next issue is about the numerator data. In order to be able to calculate reporting rates or any event rates you need a good numerator. That pertains to the adverse event reporting that we have. We listened to the limitations of this system as well, significant under-report, poor quality of reports, and then variation in the number of reports that you get as the drug has stayed on the market for a long time.

I think as physicians we are responsible for some of these issues because we don't report as many as should be reported. There are many issues that need to be addressed to try to increase the number of reports and the quality of reports.

There was also a category of comments we got on it's time to do active surveillance. I'll talk about that a little bit later. Then there was some issue also that came from the sponsor. There are four areas mainly I just want to summarize.

With respect to denominator data, exposure problems, really the comments that were received were, you know, but the lack of information about the event rates or information about background rates because you need to do a comparison to be able to assess whether a particular safety issue is significant. You need to calculate that and in order to do that you need to have a good denominator and also a good numerator.

Background rates you have to have for comparison. You might think that there is actually a lot of information about background rates for particular events with respect to a particular indication or with a particular drug with a particular disease condition. But there isn't really a whole lot of good information when you talk about pediatrics. You can deduce some of this from the literature but

you don't get exact information.

Then the other issue was how do you present the data in terms of measures of risk whether it presented in terms of excess risk, risk ratios, rate ratios, or pediatric-to-adult ratios, or p-values. These are all very good statistical issues to address. But I would like to first certify I had the right data. I wouldn't want to use such p-values or confidence intervals if I don't have good data because it's just misleading.

So when you have good data I think it's a good idea. We are trying to address those issues but it really falls around the area of denominator data problems that we have. It's an agency-wide problem. It's actually a national issue because we don't have good measures of drug exposure.

What we have tried to do in terms of looking at pediatric issues, we now have quite a large pediatric inpatient database. Our inpatient database was CHCA prior to this. We have shifted to another database which is bigger. It includes a large number of pediatric and nonpediatric hospitals. We still are

in the process -- we need to evaluate whether the data can actually be projected nationally for pediatrics. That's an area that we need to work on.

We also looked at the earlier database that we had with respect to whether there is a feasibility to projecting the inpatient data from the 29 hospitals to the nation. There were obviously limitations as to whether it's possible to do that. I don't have much time to go into the details of it but I think what I can say now is that we have determined that using the CHCA data for developing a methodology to protect the data nationally has serious limitations.

We have continued also to maintain in the Office of Drug Safety access to the multiple data sources that we have including IMS Health, Caremark, and other used databases. They have their own sets of limitations with respect to measuring frequency of use of medications in children. IMS does not have demographic data so we can't really sort out the pediatric outpatient use. We can only estimate it

based on other proportions that we developed from other datasets.

We are also working with NIH. We will participate in their efforts to get access and develop the databases that would help measure frequency of outpatient medication use using Medicaid or HMO or a pharmacy benefit organization. They have some projects that they are developing that would help us assess some of these data and the frequency of this data.

Now, the next area was enumerator which is what we discussed today in the morning as well as also a number of the issues came up today. One specific area that came from the feedback was standardizing the adverse event coding across programs to enable pooling of safety data for analysis.

This morning you heard the coding that is done under MedRA which is really a standard coding package for post-marketing reports. It's not required yet for NDA or IND. We use it routinely in trying to assess post-marketing reports so there is a system. Whether that would transfer to the trial data and make

it a requirement is another issue that maybe Min would talk about later.

There was also a comment about grading system for serious adverse events so that we can follow up on the cases for more additional information. That is actually a routine part of what the Office of Drug Safety does. When there is inadequate information there is a follow-up that's needed and there are opportunities to call the reporter but additional information may not always forthcoming. The companies do have a lot of information. We often go to the companies for additional information and they do provide that.

We have also tried to do our reviews better in the Division of Pediatric Drug Development. Our medical officers have been trained now in looking at AERS database. We are trying to make statisticians out of them and computer programmers out of them. They are able now to search for specific terms by drug for drugs that are assigned to them.

Instead of waiting a year to look at what the reports are, we can actually continuously look at

them on a quarterly basis so we can pick up early signals of concerning serious adverse events before the 15 months or so that it takes to produce these reports that we provide to you. So we are also able to do hands-on review of the case reports. We can print them and get them from Office of Drug Safety.

Now the big issue about active surveillance. Everybody says we need to have active surveillance. We all agree conceptually this is the best way to develop a good handle on the adverse events and also a good handle on the exposure so you have both sets of data to be able to collect and at least address the issue of safety. Not just in pediatrics but also in all populations.

There was a suggestion also about building on existing systems but existing systems are all either specific to certain class of drug. There are some active systems like the pregnancy registries or anti-epileptic drug exposures during pregnancies, sort of active surveillance system going on for that. There are many like that which are sort of specific to

certain drugs or certain outcomes.

But the whole issue of active surveillance really is a topic that has come to get some attention and it's under consideration by the agency. There isn't really a whole lot I can say about that but it is something that has come of age that we need to get some additional feedback from you as to how we want to focus it or what the scope should be.

We had some comments also from the committee about the sponsor issues mainly around the issues of sharing the safety reviews with sponsors early so that there is really feedback from the sponsors as well. There was one suggestion that said we should have a pre-AC meeting, pre-Advisory Committee meeting, to discuss some of those issues.

What we are doing now is that sponsors ere notified that the drug is actually going to be discussed at the Advisory Committee meeting one to two months prior to the meeting date. Sponsors are receiving copies of the slide presentation at least three days before the PAC meeting. We'll have some communication with them and sponsors have

been responsive and given us some additional information that was not in the AERS reports. It has been useful to some extent.

Okay. So where do we go from here? We have been thinking about this area in Office of Pediatric Therapeutics as well as in the pediatrics area here. We will try to present in the next 10 minutes some suggestions, some options for discussion. This is sort of a work in progress. So that we can get some reaction from you we wanted to start the discussion. We have some specific questions at the end of my presentation that we would like feedback on from you.

We have divided it up into two parts, with current resources what we can do and with additional resources what are some of the things we can do. The options that we have here are not limited to what I have. This is really to start the discussion.

Now, we have been giving you sort of full-fledged presentations on the post-exclusivity adverse event report for these drugs. Some of them give you a lot of detail and there is no safety concern. We are

just doing the mandate. It is a mandate. Remember it's a mandated activity for FDA.

So what we're proposing is when there is no safety signal that is detected or of concern, which means there are no AEs reported during that reporting period like what we've had with some drugs today, or reported AEs raise no potential safety concern. All events that have been reported are labeled or there is no increase in frequency or severity of a labeled event. Then what we do is provide you with an abbreviated written summary report instead of taking you through this whole presentation and, of course, give you the background package as well. We'll still do the reviews. We just don't present it un public because there isn't really any additional information that we can provide or there isn't a whole lot to discuss.

What we feel is that when there is no safety signal detected we will give you the abbrevated written summary, maybe a slide summarizing what the adverse event review says and then the background materials you will have in your package -- if you have

questions based on reading the background materials, we can still have a discussion. It's your prerogative, I guess.

When there's a possible safety signal detected, which means there's an increase in frequency or severity of unexpected adverse event, or there is an unexpected serious unlabeled adverse event, or there are some events that are completely unique to pediatric patients that have not been seen in adults, then we'll do an in-depth background safety review and then do a full-fledged presentation and a public discussion of the findings.

We found this to be the most efficient use of the time that we have for public discussion that we don't go through a whole litany of drugs. You are all very busy but we want to use your expertise where we feel that we need it and that we really feel we need the feedback on. We will be asking you the question later on whether this format is agreeable to you for future presentations whether it's the June meeting or the fall meeting.

The full public presentation will include,

again as I stated, the drug use, reported adverse events, pediatric exclusivity studies, reveaw of the literature, and when possible and we have the data an analysis of event incidence rates like what you're requesting, also reporting rates, and background rates.

That would be mostly coming from the literature and we will have a discussion of biologic plausibility as a discussion point and present that to you so that you can take that into consideration. I think this is one of the comments that we got from the committee.

Other options that we are considering is really a communication issue about dissemination of what we get from the safety reviews. What we are proposing is to post a summary of the safety findings and outcome of these meetings on the Office of Pediatric Therapeutics webpage so that people have easy access to the safety signals that might have been detected and the outcomes, the recommendations that came out of the committee.

For example, when you had the

recommendation about the fentanyl transdermal we would put that information on this communication website. We want to develop linkage to relevant reviews and labels so that you have easy access and the public has easy access to the information instead of going to different websites.

And we also want to publish an annual summary of the BPCA-mandated safety review results, what the police would have been able to garner from these reviews in peer-reviewed journals so that the broader professional community has access to what we're doing in these reviews.

Then I want to go now to the area where of what is possible to consider, or potential programs with additional resources. One suggestion that also was reflected in the feedback is the active post-marketing drug surveillance.

There are other things that we can do -- use administrative claims databases for doing epidemiologic analysis of specific safety concerns or hypothesis that there is a link between the drug exposure and the particular outcome.

Also enriching our AERS databases by creating linkage between it and registries, exposure or disease/outcome registries that exist. The COG group, the Children's Oncology Group, has a database that we can garner. Dr. Santana had mentioned this before in previous meetings but possibilities of looking beyond AERS database for safety information about oncology drugs.

Then the other issue is about required long-term safety studies from sponsors. Then the other AERS, active surveillance programs that already exist for other purposes, and then to increase the number, quality, and completeness AE reports is really enhancing the AE reporting.

Now, I want to focus on the first four because I feel that those are probably the most important at this moment to get feedback on. The active post-marketing surveillance could take many forms. It can be a health facility or health network-based system.

It could be a physician office-based sentinel system. A sentinel system which is cheaper

relative to having an all out sort of nationwide surveillance system so you have more focused center of reporting system that is a network of physicians and network of facilities and network of geographical representation, a center of sites that would provide information in a perspective manner.

They need to have some capacity to monitor specific populations of children, pregnant women specific outcomes for drugs. It's really a resource-intensive effort. It's not easy to do. It's very expensive relative to passive reporting which except for the analysis, coding and keying of information cost little to the FDA but the societal course is also less. This one is resource-intensive effort.

The strength of this is higher quality of data that is perspectively collected, a better handle on denominator which is a critical area and a better handle on numerators which is the adverse event reports that you have.

The limitation, if you are looking at sentinel system is that there's always a question of how representative it is depending on how the sites

are selected and what populations they are actually covering so that's a consideration in terms of active surveillance system but it's infinitely much better in terms of the quality of data and the breadth of information you get on drug adverse events, interaction, drug-drug interactions, a number of issues.

Now, what are the other things that we can do maybe to better inform our safety data regarding pediatrics? There are longitudinal databases that link prescription information. They include information about dose, duration and then outcomes. They are claims databases. Their strength is that they are population based. They get longitudinal drug data for the population.

There are cohorts of unexposed patients for comparison purposes. You can do hypothesis testing. You can do some signal detection and quantification of risk whether you measure in terms of attributable risk or measure it terms of excess risk. Those kind of things can be done using epidemiology tools. Limitations, of course, many of these

databases that exist now do not have in-hospital drug exposure data.

There is difficulty in obtaining medical records sometimes because most of these events are out-patient. Difficult to ascertain death so if there were serious adverse events that result in death, that's an area which may be very difficult to ascertain.

Now, FDA has access to some databases and there is an FDA cooperative agreement program that has been accessing databases from Vanderbilt, Harvard, and United Health, all different healthcare settings. Vanderbilt is Medicaid from Tennessee and California. And then Harvard program group is HMO network and then the United Health is an IPA.

They are considered to have limited geographic distribution. They are not nationally represented. They are really limited. The biggest probably is the United Health where we have 10 states. Then the size of the population included in these databases vary and the number of years of available data vary. The oldest is probably the Tennessee

Medicaid.

I just thought I would give you some examples of some of the analysis that have been done using FDA cooperative agreement program just to give you an idea what can be done with these data. In 2000 there was an analysis looking at cisaperide using contraindicator settings. There was alosteron use and ischemic colitis relationship, Claritin, and then an array of statin use and the risk of rhabdomyolysis.

These are sort of on a population basis. Some of the epidemiologic analysis you can do using just databases but you've got to have some hypothesis that you have a priority to look at. It's not a fishing expedition.

Then the other areas I'll just quickly go over. Linkage with existing registries. This could be exposure registries like what I mentioned before, pregnancy registries. If you have a specific question, you know, those can be useful.

Then there are event outcomes where specific outcomes are tracked, acute liver failure, aplastic anemia registries are two examples of this.

There are also cancer registries and state-based cancer registries, the SEER databases that have some information that could be helpful but they don't provide the whole answer. It's just additional sources of information that we can tap into.

Another area is sort of looking at long-term pediatric safety studies. This is another one that is resource intense. The potential program that we can have is incorporating assessment of growth as part of the safety studies in pediatrics. And then where appropriate also request long-term safety study after submission of results for exclusivity where they make it a condition. You can't make it a condition for exclusivity but it's something that you would request to have done.

(Whereupon, at 5:00 p.m. the meeting continued into the evening session.)

E-V-E-N-I-N-G S-E-S-S-I-O-N

5:00 p.m.

DR. IYASU: The types of studies may include depending on what the question is, different designed control studies, open label. It could be a cohort study or registry study. They all have their advantage and limitations depending on what question you're looking at. These are some of the areas in post-marketing studies that could be done to assess long-term effects.

I'll talk very briefly so that you have some idea what I mean by existing active surveillance systems. There are three basically examples I want to

give, National Electronic Injury Surveillance System and the Drug Abuse Warning Network, Toxic Exposure Surveillance System.

NEISS, or the National Electronic Injury Surveillance System, which is a database from emergency departments from hospitals in the U.S. All injuries from the emergency departments including drug related are captured and the strength of that is nationally representative.

There are active surveillance systems. There are medical records. They collect information by demographics by cause of injury, outcome. It's very cheap. It doesn't really cost that much just capturing the data. There's a cost center for coding this information from medical records.

Limitation, of course, the key events onset was outpatient settings so you tend to capture only the ones that end up in the emergency room so there's a limit. Most of what we get seems to be like overdoses or anaphylaxis or rashes but, nevertheless, another data resource that can be tapped into.

And then, of course, they have to be

presented to the emergency department in clinically confirmed cases. Unless a physician states that this is drug related, sometimes it's not captured in the medical record.

The Drug Abuse Warning Network is data gathered from emergency department visits. This is, again, another sample of short-term hospital visits, about 900 of them. Basically, as I said, emergency department dataset.

It's supplemented by data from 300 jurisdictions, medical examiners and coroners. This had some improvements over the years. The strengths of the system is extensive drug information but most of what we get is illicit drugs, prescriptions, and then we get the information on over-the-counter medication dietary supplements so there's a range of prescription medication over-the-counter as well as non-pharmaceutical inhalants.

High and low-frequency events can be captured here. New and old drugs and then there is, of course, a representative sample so you can have estimates nationally and look at trends. Limitations

again is incidental reporting of drugs taken for legitimate therapeutic purposes, nonspecific drug reporting. We don't have really a lot of information about brand or chemical name so there are limitations but this is something that is another database that the Government has.

Then the toxic exposure surveillance system which was begun in 1983. Mostly this is six different participating poison centers. The data cannot be projected. There's a range of information about the toxic effects, the demographics and other information about the agents.

The strengths of the system is the large number of reports, about 2 million of them. You are able to describe the patterns of poisoning by substance and demographics and outcome but there is no national projection so you can't really look at national and nationwide data or trends. Therefore, we can't really see if there is any increase or decrease in any of this.

More options. I'm not going to focus on this one but increasing the number and quality of AE

reporting to MedWatch through education, outreach to the public as well as to professionals. And then hospitals and clinics is an area we need to focus on to try to increase the reporting by the public and by professionals.

I have given you sort of a whole range of sort of thoughts about different areas that we need to focus on for your feedback. The current post-marketing data system for BPCA-mandated reporting has serious problems as we all realize. Therefore, we would just ask you for advice on how to best to provide information that is useful. As my previous boss at CDC used to say, "We have a lot of data systems. We are data rich but information poor."

We have a lot of data systems all over the place but they don't produce information that's useful. Therefore, how can we best utilize our available resources and enhance them to provide information that's useful to physicians, the public, and children.

Now we have a set of questions for you. The first one pertains to the format of the

presentation, the content. I'm not going to read this but, Dr. Chesney, if you want to read the question, or do you want me to read the question?

"OPT proposes to submit an abbreviated summary report to the pediatric evaluation committee for drugs where the one-year safety review does not raise a safety concern. There were no post-marketing reports submitted or the reported pediatric events do not provide any concern over possible safety risks.

The entire written summary will not be presented as a public PAC meeting. However, a slide summarizing the product review and our recommendations will be presented. Do you concur with this approach?"

Then the second question is sort of --

CHAIR CHESNEY: Solomon, maybe we can go ahead and address No. 1 and then move on to No. 2.

DR. IYASU: Okay. Thank you very much.

CHAIR CHESNEY: Thank you.

DR. MURPHY: I don't need to tell this committee to modify it as they need it. I know you will.

CHAIR CHESNEY: Excuse me. Any questions,

comments, reactions to the first question which is up there? Yes, Deborah.

DR. DOKKEN: Maybe this is too simplistic but I think in the first two questions that we got in the background memo it seems to me if you distinguish, as sometimes people do, between efficiency and effectiveness, I think answering yes to question 1 and question 2 probably in some ways might increase the efficiency of our work as a committee.

I guess my question is then what would the committee be -- you know, if we got better at doing this part of it and it took less time because the presentations were streamlined, you know, then to what purpose would the committee turn itself? I think we're going to stumble upon the data issue again.

To me, I guess, question 1 and question 2 are almost no-brainers because in the short-term they may help us be more efficient as a committee but we still have the big question of our effectiveness and what information do we have to meet our goal of ultimately protecting a segment of the public, namely children.

DR. MURPHY: Well, I think we are not saying that No. 1 is going to in any way deal with the underlying issue of how do we get better data. That's what the rest of that presentation was about. I think No. 1 is to try to say to you that if it's a really obvious -- as I said, sometimes we may equivocate on it and then we would probably bring it to you.

But where we think there's little use, there's no signal. If there's anything at all, it's absolutely compatible, it really does not -- we do not think it's informing anybody to go through this extensive presentation to you and have you sit there and say, "Yeah."

What we would like to do is try to abbreviate some of that so that we can put our resources into really focusing on and maybe doing more where we think we have a signal and trying to maybe bring in additional experts. I don't know. We've only had a few signals so far but that's what we're saying about this part of it. But, as we said, we have to report to you.

Not that we don't want to but we have to

do this, but we also want to make sure that you get the information. But you can imagine these people practice their slides and go through rehearsals. It consumes a number of hours when we don't think there's a signal. Now, I think the issue is how do you define no possible signal and that's going to be, I think, where we're going to have to have some discussion because I think we don't want to cut it off where actually we could have discussion.

DR. BIER: Joan.

CHAIR CHESNEY: Dr. Newman and then Dr. Bier.

DR. NEWMAN: Just a question. If we had voted yes on this, then would we have skipped the discussion of benazepril and esmolol?

DR. MURPHY: Actually, for one you would have skipped it and the other we would have probably brought it to you.

DR. NEWMAN: And which is which?Well

DR. MURPHY: Well, it depends on who you talk to but I think certainly where we didn't have labeling and where we didn't have a lot of information

and it was a difficult trial, which was the esmolol, probably we would have brought it to you just to say, if nothing else, this is why we don't think it needs to be.

Dr. Bier.

DR. BIER: Well, I think the less response is a QED but, I mean, I think to me it just depends on what's the committee's charge. I mean, if we go along this route, for example, we are basically not reviewing in detail these documents. If that's part of our charge, then we are giving it up. If it's not part of our charge, why do we do it anyway? I mean, it's not a question. Which is it? Is it part of our charge?

If it's part of our charge, it seems to me that we need to provide some formal vote on it and that would be, for example, I can see other ways of doing this. For example, us getting the information beforehand and having the written vote but then it may not be an open meeting. I don't know.

DR. MURPHY: Let me get the exact wording. Actually, we're supposed to report to you so let me

find exact wording and I'll read it to you.

CHAIR CHESNEY: Dr. O'Fallon.

DR. O'FALLON: Well, I think the idea is great but I think that we need to define the contents of the abbreviated summary report. In particular, what I would argue for is that we need to know. We have to get some sort of an idea of how many children were treated during that year, which is the one we're supposed to be looking at, so that we can evaluate -- so we see zero or one reports.

If there were only 50 patients that doesn't mean the same as if there are 5,000, that type of thing. We need to have some kind of idea of how many. Maybe it could be an interval. It would say between 100 and 200 or something like that but have some idea of how much information there is available to you at the end of the first year.

Then I think I would want to know why you think -- explicitly why you think that there is no -- does not raise a safety concern. You say the rates are very similar to what we've seen in the adults or something but that we would have some idea what's

going on so that we could argue with you if we looked through it.

I won't but some of my colleagues here will say, "Hey, I think you're wrong. This does have a signal," or whatever. But I think we have to have enough information in that abbreviated summary report in order to do our job.

CHAIR CHESNEY: My understanding was that we would still get the same materials. It's just that we would get your conclusion and you wouldn't plan to present it beforehand. Is that not correct? We would have all the same materials we've been getting.

DR. MURPHY: And it sounds like you not only would want these materials, you would want in that material a reason why we did not think we needed to report so that would be one thing we would have to add to that report.

DR. O'FALLON: You kind of had it on some of them but not all of them.

DR. MURPHY: Do you want me to read this to you guys the exact wording? The exact wording is, "Drugs with pediatric market exclusivity in general

during the one-year beginning on the date on which the drug receives a period of market exclusivity under 505(a) of the FD&C Act. In the report of an adverse event regarding the drug that the Secretary of Health and Human Services received shall be referred to the Office of Pediatric Therapeutics established under Section 6.

In considering the report the director of such office shall provide for a review of the report by the pediatric advisory subcommittee of the Anti-Infective Drug Committee (which you used to be) and include any recommendations of such subcommittee regarding whether the secretary should take action under the FD&C Act in response to the report."

DR. BIER: Well, I interpret that as meaning it's our job.

DR. MURPHY: And we're saying we agree it's your job. What we're saying is we will send you the material. For a select subset of the products we will send you the material and say, "This is our recommendation. We will put it up for a slide at the meeting."

Then having had read the material you disagree, then we would still have a discussion. We would not go through a slide presentation summary. What we would do is we would take the other ones where we think there's an issue and we would try to expand upon those some more. But you're right, you do need to still read the material. It's not that we wouldn't send it to you.

DR. BIER: So fundamentally what this saves us is a 10-minute presentation. I mean, you have to do all the work. We have to do all the work, we have to do all the work, so basically what we're talking about is saving a 10-minutes presentation. That's fundamentally it.

DR. MURPHY: It's not a 10-minute presentation.

CHAIR CHESNEY: Can I give a different interpretation? I actually think there's more responsibility on the committee if we don't anticipate a full presentation than when we do because when the responsibility is on us to read the material and raise the issues, that's much more fearsome to me than just

sort of flick through the issues and listen to you and see what you say. I almost think that it puts more responsibility on the committee if we have to raise the issues and you just give us a summary slide. That's just my interpretation.

Dr. Newman.

DR. NEWMAN: It sounds like from the description of what we're supposed to do is that reviewing the studies that were done to get the exclusivity isn't actually part of that. For me those have been the studies that have raised my concerns.

It wasn't the one or two or three adverse event reports which I find very, very hard to interpret. It's the studies that actually had a denominator and there were 100 kids and a large number of them have adverse events. I guess the question is do we -- will we at some other point review those studies done to establish exclusivity and demonstrate safety and efficacy?

Or, if not, who will? I don't mind letting go of the -- leaving to you guys the interpretation of the few adverse reports that trickle

in but the exclusivity studies have been what have raised my concerns.

DR. IYASU: Could I respond to this? I think there has been a history. We have had -- I think this is the 6th presentation that we've had. There's been feedback that we've been getting from the committee as to the usefulness of the presentations that we've been doing. As I said in my presentation, we've enhanced the presentations to add more interesting information about the studies that have been done for exclusivity.

It seems that they have raised a lot of questions. I think they have been useful discussions but with respect to the specific charge of this committee with respect to Section 17 of the BPCA, it's really the one-year post-exclusivity period that is of interest.

Now, we're doing more than what the charge says so whether that is -- whether you want us to continue doing that or not is another issue that we maybe need to get some feedback.

DR. MURPHY: Well, I guess my question,

Dr. Newman, would be the division has reviewed the studies and has made a decision on the efficacy and safety. We provide some background material in the summaries to put in context what was there during controlled trials which is the best you are going to have and we would continue to do that.

I guess the only other thing would be does the committee want -- I have to follow up on if we can give you the unapproved ones but does the committee want the entire study submission because that's enormous and I don't think you want that. I mean, you may but it would be many, many, many volumes and line listings of every page. You know, it would be just voluminous and I don't think we could actually do that except for on an exceptional basis where there was some focused question.

But we can give you the more extended review and the summary potentially but, again, the complete review, you are getting the summaries, are also quite extensive so I don't think as a routine you would want those but I shouldn't be -- I'm just telling you what's in them so you understand.

CHAIR CHESNEY: Could I ask how many people find -- what Dr. Iyasu is saying is we did not used to get the exclusivity studies and I found them very interesting and helpful and very much provided background on which we can put the adverse events such as they are. I guess I would like to suggest that we continue getting that information even if we agree with question No. 1. I wonder if other people have thoughts about that.

Dr. Bier, Dr. Moore, and then Dr. Gorman.

DR. BIER: The less information you give us the less likely it is we will be able to come to a decision about anything.

CHAIR CHESNEY: Dr. Moore.

DR. MOORE: Well, I think we've gotten our charges confused here because in the first two drugs we looked at the controlled studies and some of us were disturbed by the adverse events that were reported in the study and sort of extrapolated that and used that as a rationale to continue monitoring this drug rather than taking the adverse events that were actually reported during that year period of

surveillance which were not particularly disturbing or asymmetrical with the adult reports and using that as a criteria.

I think one of the things we've done today I think the FDA staff here has given us very consistent recommendations but we have been inconsistent in how we've decided to either recommend or not recommend continued intensive monitoring. The first two drugs if you look at just the -- not the studies but the adverse event reports, they are not at all asymmetric numerically, nor are they qualitatively different than the adult reports.

I would say that we should then consistent with our charge agree with the FDA recommendation, with the staff recommendations when we didn't. Then we went to the next drugs and did just the opposite because we weren't as concerned perhaps about the controlled studies. I don't know.

We either took the recommendation where the FDA said take it, or we didn't take it because we weren't particularly concerned about the controlled studies. They looked like they were better powered

and the data was more reassuring to us. I think we have to decide what the role of these -- we are going to be provided this background which I like. I'm with everybody.

I would like to see that. I think we have to decide how that's going to impact our decision and whether it should. It was my understanding it's not supposed to particularly. It's already been reviewed and some other people have said, "Okay, that's how we categorize this drug to begin with and now we're going to surveil it." We're reviewing the surveillance part.

CHAIR CHESNEY: I think you've made a very good point and I think for those of us who have been on the committee for a while, we picked up on that immediately because all we've seen before is that one year. We never saw what came before it. I think it's helpful to see what came before.

Just because we don't pick it up in the one-year post-exclusivity, if it was serious during the studies, then it may be just that we need to look at it for another year. The reporting is so sporadic

that I sort of came to grips with it. I realized where you all are coming from but I think that was one reason we asked for the studies that were done for exclusivity is that we had no idea what the background serious events or nonserious events were. At least now we know what they are.

I think what we saw, with the first one anyway, was that there was a background of serious events. Even though we might not have been worried for this year, there was enough concern that the reporting system is inadequate enough that maybe we need to look for one more year before we are confident that it's not -- that these are not going to show up later on. I guess that was how I came to grips with it.

Dr. Gorman.

DR. GORMAN: To amplify on both of those responses, the other value to this committee, and perhaps to the FDA of presenting the exclusivity trials, is to listen to our comments about their shortcomings as you continue to evolve to make those trials better and better and to get the information

that we all want.

DR. BIER: I just -- you know, I don't think any of us on the committee want anymore work. I certainly don't want anymore work. What I want to do is to satisfy precisely what the statutory requirements of my participation on this committee.

I think this discussion here right now has made it a little bit uncertain. If you can concretize that in a very precise way about what this road is about, then I'll have a better understanding of whether I need this or not. That's where I am.

CHAIR CHESNEY: Dr. Garofalo had a comment and I'm sorry I left you out. Then we'll let Dianne respond.

DR. GAROFALO: I just wanted to add that it's often helpful to look at the controlled trials when you're looking at open-label uncontrolled safety data so you have come comparison because it's the controlled trials that really have the adequate group to compare.

In addition, sometimes, you know, an extension of that would be what did you see in adults

that made you believe that the children looked like the adult data. That's always helpful just to set the context but I don't think you want the detail and the amount of detail that we provide is really extreme.

The other comment is I think it was noted earlier that there was an adverse event rate of like '94 percent but I would submit that if children are very sick or if you watch them for a very, very long time you'll get very high adverse event rates. The rate per se in open-label studies is maybe not useful. It depends again on compared to what else.

CHAIR CHESNEY: Dr. Glode, did you want to comment before Dr. Murphy?

DR. GLODE: I just want to go back to that exact issue. It seems to me that we could reduce the volume of material because there's a lot of repetition in here. All I want is I want death -- well, I want the controlled trials and I want a comparison table that shows it in the adults, just exactly what you mentioned so I can put it in context.

Then I actually only care about death and hospitalization. I don't really care about minor

issues. I think that death and hospitalization actually will pick up morbidity, significant morbidity, because I'm going to think most significant morbidity resulted in a hospitalization, etc., etc.

I think the passive surveillance system is so bad that it's uninterpretable so that's why we've got to have, I think, the controlled trials to just say, "Does this drug look like it has a lot of side effects?" The fact that we didn't see anything in the possible 150 children or 4,000 children or something that nobody bothered to report it.

I mean, I don't want to tell you how many times I've not reported to the FDA an adverse drug event. I'm an infectious disease doctor and I'm not going to discuss that any further but I think there's massive under-reporting.

CHAIR CHESNEY: We know how massive it is because we don't do it. It has to do with the length of the form and it has to do -- I said to Dr. Iyasu before -- with the follow-up call that you know you'll get. You just think, "I can't handle it so I just will know it myself and tell my colleagues about it."

That's horrible but I don't think there's anybody on the panel that wouldn't say that's exactly what they do so we know how bad it is.

Dr. Murphy, would you want to respond to Dr. Bier's very precise question?

DR. MURPHY: Now let me make sure that I know what the precise question was. Can we make it more concrete what you're supposed to do statutory-wise?

DR. BIER: If we are only supposed to vote on the post-marketing studies, then that's all I need and have to vote on if that's the question. If we're supposed to make a judgment about how good it is relative to what else is available, then I need more information. I just don't know.

DR. MURPHY: We interpret the statute to say that they want us to look at the post-marketing. We also don't think that Congress is full of a bunch of scientists so we don't think you're going to be able to extract a whole lot if we just give you the adverse event reporting. We have tried and are still trying.

This is an evolving thing that you have a lot of input into. We are trying to get to what we think was the intent -- Rosemary, help me here -- which is we think they wanted to make sure that if a product was studied in children and, therefore, got approved, though it's actually not, as was said, there would be more use and that we are looking at that after that product is out there and being used.

We think it was a safety issue. They wanted us to make sure that somebody is looking specifically because we know the reports don't come in specifically broken down for children on what the safety or what the risks are that kids are being exposed to by now taking these products. That we think is what they wanted but that's not what the statute says.

That's our problem. Okay. So we are trying to balance just bringing you adverse event reports which, as Dr. Stockbridge said as he walked out, to keep looking at the adverse event reporting isn't going to help in some situations when the numbers are really low because you're just going to

get more low numbers.

We're trying to construct a positive process out of a very limited database, as Solomon said. We've got lots of data but we're not sure how to make useful information out of it so that's what we're trying to do. We thought that giving you the trials would help you put it in context. As I said, it's already been reviewed.

We can't go back and relabel it because we took another interpretation out of the trials. Then you would have to get all those volumes. What we can do is know whether it showed up in the trials. I think the committee is getting to some of the things we need to hear which is what you really want to know.

You want to know the trials. You want to know the severe, the definition that you got this morning. We've been trying to do that and we had actually an internal discussion about you don't really need the 10 top 20. You need severe.

You've been getting the 10 top 20. You don't need the 10 top 20. You need the severe. Okay? Then you want that compared to what's going on with

the adults. You need it compared. We've been trying to do that for you. What's in the label and what's not in the label.

Then what I heard today was something we were trying to think about for expanding this is doing more background information on what happens in this disease normally, how does this fit in with that disease, is this really what we would expect. Trying to do more of that kind of work on the ones where we think we're seeing something.

I think what we're trying to get from you is where it's sort of a "duh" situation as the kids would say. What's the definition if there is really no need to go through the whole litany process with you on everybody's products because we've done 34. There are 117 now and we just think there ought to be a more intelligent way of doing this. I guess that's what we're trying to get at.

CHAIR CHESNEY: Dr. Santana.

DR. SANTANA: Can I get a point of clarification? As you were speaking I was referring to the slide in terms that this is also a public

process where people that are not at this table but are sitting behind us or read documents outside of this area get the information.

Are you making the recommendation that if we just get a brief written summary for these that there's no signal or there's not enough post-marketing reports to suggest any issues, that the summary of the product review, your slide summary, and your recommendations would also be posted for the public to read?

DR. MURPHY: Yes.

DR. SANTANA: Because, if not, they would have no other access. Am I correct?

DR. MURPHY: Yes. They would all be posted. Anything we send you in a background package is posted after it's redacted. I specifically explained it's only redacted if there is some of that CCI information or stuff like that in there. The information would be posted.

CHAIR CHESNEY: Can I suggest I think we're very interested to get to question 3 because whatever we do with 1 and 2 is like moving deck chairs

on the Titanic. If the committee could agree that we support your suggestions for questions 1 and 2 so let me ask if anybody is not supportive of what the FDA suggest for questions 1 and 2? Does anybody not agree or not go along with their proposal?

DR. SANTANA: Dr. Chesney, for the record you need to redact this action to include the recommendation that the report should include why the FDA does not think the signal is -- the data is not of importance that it needs to come to the full committee because that's not in this question as it current is so I would vote for your comment if that was added to this question.

DR. MURPHY: And I would like to say why it doesn't need -- not extensive but why it doesn't need a further public discussion beyond the opportunity for the committee after it has read the information to say it does or does not agree. We are really just cutting out our presentation is all we're doing and we are sending you the material.

CHAIR CHESNEY: So I think -- Dr. Newman.

DR. NEWMAN: Yeah. I have a comment that

I was saving for when we talk about question 2 but I guess we're skipping over that, and that is to agree with Dr. Gorman about trying to -- that the usefulness of getting the exclusivity trial data and trying to improve the process.

I think an easy thing to do -- the easiest no-cost thing to do would be to just improve the presentation of the adverse effect data of the trials that have already been done. When we saw the data about Clarinex what we got were just absolute rates that were more than 2 percent in the Clarinex group and we didn't get any p-values and we didn't get any confidence intervals and we didn't get any rates in the placebo group.

Just for question 2 it says the data will include assessment of incidence, but in your slide you actually have getting the excess risk and the risk difference and the 95 percent confidence intervals and the p-values all of which for clinical trial data which we are being presented would make them interpretable. I want to make sure you get that feedback for trials that have been done, randomized

trials. We need rates in the placebo groups and differences and statistical significance.

For trials that are going to be done I think the case of benazepril really illustrates that we would like to have comparison groups if we are looking at safety so we can see whether these effects are happening more often than they would with placebo or with some other drug.

DR. MURPHY: That's great and we can do that. The only problem here now, remember, and I think we did point this out to you guys, that in the hypertension template they have an option of how to do the trials and one is with the comparator and the other is the dose. With the dose there is no comparator. The dose --

DR. NEWMAN: and this is something we can't fix?

DR. MURPHY: I will tell you that the division feels very strongly that a good dose-ranging study that shows PK/PD effect in a way that is statistically significant and one is as good as a comparator, at least for efficacy, your problem is

it's not going to be powered for safety.

We don't power the trials for safety. I should say that. There probably are some but I'm just saying in general you're not powering it. There may be a safety endpoint in there sometimes but the efficacy endpoint is usually the driver of the statistical design.

Rosemary, do you want to add to this?

DR. ROBERTS: There have been numerous discussions with Cardio-Renal. There's been actually work on the template. The thing is, yes, you're right. We would like to have comparative safety data. As soon as you put in a comparator arm, you increase your numbers astronomically if you're going to try to show that it's as good as another drug on the market.

Now, we're at the point where we could do that because we now have some antihypertensives approved in the pediatric population and some approved in the various classes of antihypertensives that are used in the adult.

This template does date back to 1998 and early 1999 when we didn't have antihypertensives

approved in the pediatric population so you couldn't really set up a comparator-designed trial. Now that we have them you could do that but it's going to increase your numbers and that's always a problem when you have to increase the numbers in the pediatric population.

The other thing is that the dose ranging study can be a very effective way of doing it if there's a dose response if you can hit on giving them a low dose that you can ethically support and a high dose that you can ethically support and then show there's a response.

One of the options is a placebo in the dose response. We just don't have takers. You're not going to get physicians to agree to put a child with hypertension on no therapy. Even as you look at the study that we saw today with benazepril you had everybody put on forced-titrated up for a four-week period of time and then they were randomized to either the drug of interest or do placebo and had a short withdrawal period of two weeks.

Now, you could say, well, we've had some

comparison of safety there. The problem is there was no washout period so you had very little time where you really were comparing it to placebo. Again, this is an ethical problem. Nobody wants to leave these children off antihypertensives for a significant period of time.

So we are always trying to find a study design that allows us ethnically to look at the condition in the pediatric population and that we certainly would appreciate if you can help us as we learn through the trials that we have seen to date some of their shortcomings because there are certainly shortcomings.

CHAIR CHESNEY: Dr. Moore.

DR. MOORE: Just one quick comment. As you pointed out, some of these pediatric studies in particular are very underpowered for safety. I think that's what the mandate we have here is. We're not reviewing efficacy at this point. We are reviewing safety. Are we not? So to me providing these studies is very incomplete, particularly the ones that are very underpowered. We are also provided with the

adult studies.

If we're going to look at these controlled studies and we look at one study on benazepril that shows 64 patients and we're supposed to consider safety, that is as poor a dataset really as the adverse events that were reported for the last year.

I think we are getting our mandates here all confused in my opinion. If you're going to look at safety, then, okay, let's look at the adult safety data that is available. Let's look at the pediatric trial as well. Then let's look at the adverse event reports. Or maybe we should just take the more limited purview which is just the reports which it seems to me is more directly our obligation to review what the reports were, not the studies which have already been reviewed and labels produced, etc.

DR. IYASU: I think this is all very good but I think I have to say, and you may correct me, we would like to use the expertise I guess to look at all the pediatric exclusivity studies but you also I think rightly pointed out about the mandate. The focus is on post-marketing.

We are allowed to have an input as to what some of the deficiencies with some of the exclusivity studies are but it's not really providing the adult data, the pediatric data. This is a who new meaning for any particular indication to track. We cannot possibly give you the entire information so that you can make those kind of assessments in a small presentation like this. I don't know. Dianne, do you have any options?

DR. MURPHY: I think if there is a problem, if we see something, that's where we would potentially go back and pull in more information because, as Solomon said, for anyone of these products they spend all day going over the safety issues for that product and for us to think that we can do that in this short period so we're trying to sort out for you.

That's fine if you don't want to do that. We are trying to make sure we don't miss -- that we are not negligent in our reporting but we are trying to focus on where we think there might be problems and try to bring additional data and have a more extensive

discussion of that because, again, if we see something, we're going to want to go back to not only the pediatric trials but the adult trials.

We are going to want to try to get information from wherever we can and bring it into you. That's where we're trying to go, as we've been pointing out, without really being negligent as to what the law says which is we bring the adverse event reporting to you.

DR. ROBERTS: Let me make one comment to sort of follow up with Dr. Moore. I was wondering with the presentation you had for esmolol this morning, I think it was you, Dr. Newman, who was concerned about the fact that there was 92 percent of the patients had one AE or more.

Now, if you look at the labeling in the clinical trials that were done in adults, 25 to 50 percent of the adult patients had hypotension. Some of it symptomatic, some of it asymptomatic in the clinical trials.

Precautions talks about the fact that this particular drug if it extravasates is very irritating

to the vein and it talks about something like 10 percent of patients having some kind of reaction because of extravasation.

If we had indicated that there is a high percentage of adverse events that occurred in the adult clinical trial, would that have helped you have some perspective on the 94 percent that we saw in the pediatric population? The other thing is it's indicated for the treatment of SVT. It's indicated for intra-operative hypertension and post-op hypertension.

The examples that you saw in children, these happen to be the children that had severe problems and went on to die but it was aortic stenosis. It was a hypoplastic aortic arch. These are conditions where you have got to get that blood pressure down or you're going to blow whatever they've done in the surgery.

These are very ill patients. Remember, for it to be considered an adverse reaction, it has to have the possibility of being related. The fact that it's just being used when a child is having difficulty

already does that. Many of these are related to the pharmacologic action of the drug. The drug is to bring the blood pressure down. Sometimes it goes down too far. If we brought that kind of information to sort of put it in perspective, would that be a help to you?

DR. O'FALLON: Yes. I think that's what Dr. Glode said. They would like a comparison of the severe adverse affects in the adults as part of their reporting.

DR. MURPHY: I didn't mean to usurp that answer but we did hear, I assume. Is that correct?

DR. GLODE: (Nods.)

CHAIR CHESNEY: So with those two caveats you just articulated and what Dr. Santana brought up, is there anybody on the committee that has any other issues to bring up with respect to the recommendations on question 1 and 2? All right. So can we move ahead to question No. 3? Do you want to read that, Dr. Iyasu, or just project it maybe?

DR. IYASU: Question No. 3, "The limitation of the spontaneous post-marketing adverse

event reporting system are well known to you. Let's discuss and prioritize potential programs assuming additional resources were available to supplement and/or overcome the limitations of the spontaneous reporting system for assessing and monitoring safety of marketed drug products in the pediatric population.

Some examples of potential programs include population based active surveillance, analysis of claims databases like UnitedHealth, Harvard Pilgrim, Tennessee Medicare, TennCare, exposure or outcome registries and creation of linkage with AERS.

Then long-term pediatric safety studies to assist drug adverse events including assessment of growth and development. Discuss if and how prioritization of products for additional long-term studies might be approached."

CHAIR CHESNEY: So this is our opportunity to make recommendations to the FDA as to how we might get better denominator and numerator data for this committee and for everybody to use to draw conclusions. No recommendations. The meeting is over. (Laughter.)

Dr. Newman.

DR. NEWMAN: Well, I think my first choice and probably the most efficient of those would be the analysis of the claims databases because I just think that those data exist and whatever you can negotiate will be a huge improvement over what we have.

One of the things that is not on there but Dr. Chesney's comment makes me consider is consider the possibility of streamlining the adverse event reporting system so that people don't mind doing it. I'll have the additional information be required of some random sample of the report so that you wouldn't necessarily get this treated phone call or something where you just make the process less onerous in order that you can get at least something for better numerator data.

CHAIR CHESNEY: Dr. Glode. Oh.

DR. SANTANA: As a follow-up to that, you know, one of the problems I have with MedWatch, and obviously in oncology if it's commercial MedWatch and if it's research to do the NCI stuff, but one of the things I find difficult with MedWatch it requires a

lot of narrative that you developed.

That's where you get into these troubles of having words that may or may not mean the thing and the assumptions are made that maybe diarrhea is the same thing as loose stools in the other column. You know what I'm getting at? I think one of the things you could think about in pediatrics, if you were going to rev up the MedWatch reporting for pediatrics, is to create a system that was more specific and not as open to interpretation so that way the data would be stronger and potentially cleaner because it's been a difficulty.

You saw it today when you had the columns of the different things that were being reported. I think something that I would recommend if you were going to take this a step further for pediatrics and kind of create a MedWatch reporting for pediatrics is to make it very user friendly and at the same time the information was consistent across categories. It was not based on what I wanted to say in that report. That's a very general comment but I'm just thinking out loud here how you could improve on that.

CHAIR CHESNEY: Dr. Glode and them Dr. Gorman, Dr. Bier.

DR. GLODE: In just sort of thinking about active surveillance, I mean, one question that comes to mind is whose responsibility is it to assure that this is a safe product for children. I guess from your presentation I was kind of thinking that you thought it was the FDA's responsibility. I'm kind of thinking it's the industry's responsibility or both, shared responsibility.

The simple way that I think about it is sort of something that's in between a registry and active surveillance. Maybe it happens at the pharmacy so now you go get the drug and you get a little letter from the company who produced the drug that says, "This drug has just started to be used in children. We would like your permission to contact you twice a year just because we are very concerned about drugs in children and being ultimately safe."

Again, all you care about when you are contacted -- "And we will ask you less than 10 questions at that time which is how old is your child

and are they still taking the drug? Have they been hospitalized in the last six months and are they alive and well? Do they have any new diagnoses? Thank you so much for your time." Click.

You know, because I feel like I'm not serving the general public or the Government of the United States with the current information that I'm receiving. I am not capable of being assured in any way about safety with the passive surveillance system. We have to get better information.

CHAIR CHESNEY: Dr. Gorman and then Dr. Bier.

DR. GORMAN: I think that I would vote for the population-based active surveillance. Let me explain why. I think that I agree wholeheartedly with my colleagues around the table who have talked about deaths and serious life-threatening events as reports we want.

But review of the data that we are going to look at tomorrow and some of the discussions today give me another group of people I really want to get which is when it raises the rate of common events

higher than the background noise.

I was thinking about hyperpyrexia which we are going to be talking about a little bit tomorrow which I don't think anybody would report on a MedWatch because it would only be seen in a controlled trial in the sense that if the rate of fever in children went up with a drug, you wouldn't get that looking at only deaths or serious adverse events.

The other group which I would really like to somehow get noticed is when your life is more miserable on your drugs than it is when you have your disease. I'm thinking about hypertension which we talked about today and that 10 percent of people had adverse events.

Most adults with hypertension are perfectly happy right up until they have their life-ending event but they are happy people until that time. It's the "silent killer." I love how some names stick.

The "silent killer" because you're happy and it's silent right up until the time you have your -- so you put people on -- if you put pediatric

patients who are going to live for 50 years on a drug that decreases their quality of life over 50 years versus the shortening of their life, I don't know where you would talk about that as being an adverse event. I don't even know if there's a vocabulary to talk about that.

I'm sure people on the antihypertensives and cholesterol-lowering agents have a decreased quality of life. Maybe it's longer. Maybe it's both. I don't know. Looking at the population-based active surveillance because I would then have the control group to look because I would have a group of people on agents and not on agents. I really want it to be population-based.

I don't know how big a population -- this is not my area of expertise -- that you would have to keep actively surveiled. It would be the hypothesis-generating group for all the other data systems that we are considering so you could look at the Framingham equivalent study for the active population group to then look at the bigger population ones.

CHAIR CHESNEY: Dr. Bier.

DR. BIER: Well, my opinion on the options is yes. I mean, any are better than none and the ones that are likely -- I think priorities should be the ones that are likely to be achievable in the political, social, industry context by the appropriate parties working together to find solutions that are actually applicable.

As far as whose responsibility it is, I think it's the responsibility of adult people to take care of their children. In this case we're talking about the people which is presumably, you know, our representatives in Congress who have this responsibility and the people who make the drugs. I mean, I think they have a more direct -- you know, maybe a more immediate one but that's the responsibility of us independent of this committee.

Then as far as long-term safety studies including growth and development, I think except for drugs that may be used for a very brief period of time and a limited circumstance I think without long-term growth and development endpoints, you know, you are not evaluating pediatric safety. I don't see how you

can if you're talking about chronic drug use.

CHAIR CHESNEY: Can I comment? I think that when I responded, and I didn't do reply to all so none of the rest of you saw my comments, but I can't help but think that this has to be a population based active surveillance.

When I think about the little experience I've had with infectious diseases that we really didn't learn anything about until, for example, toxic shock syndrome and penicillin-resistant pneumococcal disease. We really didn't understand the extent of that until the CDC did active surveillance with selective populations.

I was intrigued -- just two other points. I was intrigued in looking back at the notes from the October 2003 meeting that the SEER program was actually mandated by law and states that every state had to develop a system whereby they follow patients with cancer and they have to be reported so that was very intriguing. I mean, if we have to report cancer maybe there are some things we should have to report about children.

What was my third point I wanted to make? Oh, I would say that the FDA is not the only stakeholder in this. I think that all pediatric organizations have a major interest in this. All the pediatric pharmacists would be interested in this kind of information. Children's hospitals would like this information because they would like to minimize and learn more about side effects and so on.

I'm not expressing this very well but I think in my comments I wondered if it wouldn't be worthwhile having a group of organizations get together and pool their ideas about how to develop some kind of population-based active surveillance program. I know at the October 2003 meeting we talked about the NICHD program that is being developed. I think it won't go live until 2007 to monitor a small population of children for everything forever. (Laughter.)

I don't think that's feasible and it's too long to wait. I'm just wondering if it wouldn't be worthwhile getting other pediatric organizations together with the FDA to pool ideas and see if there

isn't some way to come up with a population-based active surveillance program to look at not necessarily just adverse events, although I think that this is a very important area.

I don't know how else -- maybe somebody could explain to me a little bit more. Tom, you mentioned that you like the claims databases. Why do you like that? Do you think that really gives the kind of information we're looking for?

DR. NEWMAN: I'm not positive what is meant by claims databases but in my research I'm actually using data from Northern California Kaiser Permanente which is, you know, very rich data source that has laboratory values and diagnoses and hospitalizations and medications and so on.

I don't know what the rules would be for negotiating that and confidentiality and so on but access to that kind of closed system where you know who is in the system and who got the medications and can look at hospitalizations for adverse events and even laboratory evidence of adverse events and so on seems to me very efficient if the logistics could be

worked out.

CHAIR CHESNEY: Dr. O'Fallon.

DR. O'FALLON: I tend to be practical. I think that it's probably going to be easier. We could enlist those claims databases faster than we could start an active surveillance but I think the surveillance is -- of course, the population is better.

For a practical thing again, people don't remember what happened six months ago so if you are really going to be doing something like this, this is going to be requiring that they be asked like two weeks or four weeks after they fill the prescription or whatever it is for this.

Since we're talking about these drugs that are being approved in this setting, it has to be something where they are asked very soon afterwards in order to catch some of it. Then there would be later on ones that would catch the bad stuff that happens later. I think they have to be -- it's not twice a year. It's got to be like at four weeks and at nine weeks or something like that, that type of thing.

DR. GLODE: But, see, I don't care about diarrhea or vomiting or rash. I think you would remember if your child was hospitalized in the last six months.

DR. O'FALLON: You'd be surprised.

DR. GLODE: I might be surprised.

DR. O'FALLON: You'd be surprised.

CHAIR CHESNEY: Other comments, reflections, recommendations? Dr. Fant.

DR. FANT: Yeah. I'd just like to second the comments that you brought up. Basically what I've been hearing is that we're struggling to figure out how to better fulfill our charge given the resources that we have available to us now which we all agree are insufficient to fulfill our charge.

In conjunction with doing that trying to do our job the best way we can with the resources that are available to us and how to improve that, I really think we do need to try to push the envelope in terms of defining what would be the best way to do it and do it however that's affected.

It goes beyond what we currently, or the

FDA is currently charged with or allowed to do under current regulations, if we have to invent something, then we need to add a little push in that direction so that five years from now we still aren't trying to simply figure out how to do our job in a less than optimal environment.

CHAIR CHESNEY: Dr. Newman.

DR. NEWMAN: There are probably people who know more about it than I do but I think the vaccine adverse event reporting system is an example of a system that involves some collaboration with HMOs and reporting data specifically on adverse effects of vaccines so, I mean, something like that for other drugs might work.

CHAIR CHESNEY: I feel like the good news is that the FDA has made for all of us major progress in recognizing how important children are. I think this would be a logical next step. If it means making it a law, then let's do that. Talk about pushing the envelope.

DR. MURPHY: Let me try and say what I thought you said and then people can pitch in and

correct it. I heard that everyone feels like they have been given a mandate by Congress that they are having difficulty fulfilling because of the limitations of the adverse event reporting system and the fact that we can't do but so much with it.

Therefore, you have suggested that it's okay for us to try a pilot, if you will, this new system where we are going to try without any additional resources, trying to redirect some of our resources, this is manpower resources, additional information analysis to put in to situations where we think there is a signal.

That, I should say, also means we may be throwing in another committee if we have to like Cardio-Renal or whatever. Okay? Those are more difficult to put together so it may be a step thing but that's what we hear about the first two questions that you got.

The second part was that clearly we need to have better systems available to enhance safety reporting which Congress thinks that they have provided us with this section of BPCA. To do that we

need to be looking at -- I'm going to say this one way and you can correct -- where we think there is a signal we need to be looking at additional places for information.

The most immediate place would be to be looking at claims databases and see if we can data-mine some of that. In addition, you're telling us that we need to have an active surveillance system which is not something we can control but we can send back this message that we need an active surveillance system because we need that kind of comparative process in addition that needs to be prospective and all the other things that go along with that.

Those are the two big messages that I would summarize. The third would be if we can't fix it, if we can't get some of these in, then there needs to be better legislation because you can't do your job the way it is right now. I just wanted to make sure I got the messages right for how we --

DR. NEWMAN: And also streamlining the adverse event reporting. Point and click.

DR. O'FALLON: Oh, for heaven's sake, yes.

DR. MURPHY: I did put a star by it.

CHAIR CHESNEY: I think, as Dr. Santana pointed out, if you could go on-line and in five minutes tick off -- there is a long list of the adverse events associated with that drug and then a place where you could put in the ones that you saw that wasn't associated with the drug. And then other places where you could just put in an X and tick it off and we might be more likely to do it.

I think that was an excellent suggestion. I know you can't guarantee we won't get a follow-up phone call but a follow-up e-mail. Could you expand on the following points that you made because then you can do it on your own time and you're not in the middle of rounds and having to go back and look at a chart and what not. I think that was an excellent suggestion.

DR. MURPHY: I think we should take additional comments from you guys just by e-mail about ways -- we don't control that, as you know, but I think if we can synthesize what you're telling us and send it to the Office of Drug Safety, it would be good

since that's been brought out for people to come up with their thoughts about ways to modify the MedWatch or the passive reporting system.

CHAIR CHESNEY: Deborah, you had a comment?

DR. DOKKEN: I didn't want to lose what Dr. Glode said later which is -- and it may somewhat tie to some of our discussion tomorrow but if there is a way to bring consumers, specifically in this case, parents into the reporting picture, to me that's going to necessitate, as I say, some of what we're talking about tomorrow about how do we communicate about certain things because they can't report in a vacuum of knowledge.

Those are certainly important stakeholders. That may be an example of something that could be done on a pilot basis. Take, you know, some smaller identified group of parents with kids and see if it's possible. I just think we underestimate what they could do.

DR. MURPHY: I would probably repeat that tomorrow when the audience is going to be bigger.

DR. GLODE: I just have one question. Is it fair to say that part of the reason for the existence of this committee is to say that we should not in general extrapolate safety of a drug in the adult population to the pediatric population or presume it so that we are -- somebody's charged. The FDA is charged with assuring safety of the drug in the pediatric population so, therefore, your exclusivity studies, at least, are not powered to show safety. Where are the safety studies?

DR. MURPHY: I hadn't thought of it that way but it is for exclusivity only that we're mandated this. However, I think clearly as you develop processes in the systems if they're good you would want to apply them more generally. We hope that some of our pediatric studies -- we do have a few large studies that are for safety only.

As you know, the ibuprofen was 40 some thousand kids so we have had a few large. We've had -- how many kids are in on the Cipro long-term follow-up? That's a very intensive long-term. It's not the number so much. It's a very specific monitoring

that's going on. Where we have already a very defined issue we have tried to have those incorporated into the written request.

I think there is a separate issue here. The safety reporting is one activity but as a pediatric committee then, you know, if you are having a lot of problems with some sort of trial issue that you see coming up all the time, certainly we can bring that up, too. We can try to develop that issue. We just would need to know that issue if it's related to a specific product or class and we have to get that group involved also.

CHAIR CHESNEY: I think this morning's discussion helped me to understand a little bit better how you set the stage for companies to do the pediatric studies in order to give them exclusivity but in the antidepressant meetings I think it just became very obvious that they were done differently than some of the other studies.

In other words, maybe the requirements weren't as stringent for a company going in to do pediatric studies for exclusivity as they would have

been had they taken them right from day one. Does that make sense? We didn't have PK data on some of the studies and we didn't have -- we just didn't seem to have the same amount of information for the studies that were done for exclusivity as we did for those that were done just to do the study. Am I expressing that correctly?

DR. MURPHY: Well, I guess I'm confused because the only pediatric studies were done for exclusivity. All of those studies were done for exclusivity. Not all but -- I think almost all of them. For the antidepressants they were all exclusivity studies.

CHAIR CHESNEY: Well, the TAD study.

DR. MURPHY: The TAD study is an ongoing study which, again, I think we've all learned from what happened in that process, but my take on the exclusivity is that, as we said earlier this morning with the SSRI trials, was that they didn't think that was an issue.

They had already gone through it with the adults and had done multiple analysis, multiple

studies, and really didn't have those specific questions keyed in and termed in the way that they wanted them after they found out there might be a signal so they were having to go back and try to retrofit those terms and make sure the terms were all being used the same. That was what I think happened.

CHAIR CHESNEY: Yes, and I understand that they were all exclusivity for the antidepressants but I mean compared to other drugs. In other words, if you had started out brand new to do an antidepressant study, you might have done it in a much more rigid and controlled fashion than the studies that we saw that were done as a result of wanting exclusivity. Help me, somebody.

Am I making myself clear? In other words, if you were going to study a new antihypertensive you would do it right from day one and you would do it with fairly well-defined criteria. Whereas I didn't feel like the studies that had been done for exclusivity were done with that same degree of rigor.

DR. O'FALLON: Rigor?

DR. MURPHY: I think one of the issues

there, again, is that with some of the cardio vasculars you have a more pharmacodynamic endpoint in addition to the clinical endpoint. You may be able to measure but with the antidepressants we don't know except that you have too high a dose or too low a dose. There isn't that nice measurable pharmacodynamic endpoint. So you're right in that they didn't have those imbedded in them.

CHAIR CHESNEY: And they didn't have PK data, for example, for some of them. I mean, it seemed like they had just done the very minimum that they had to do. I don't mean to draw this out but I had the feeling after that that their criteria for exclusivity studies might be different than those for somebody coming in out of the blue and wanting to do a new study.

DR. MURPHY: That's what I'm trying to say. I hope they're not. I hope they're not. I think it's built on what other information you have at the time and that's the problem is that sometimes those studies don't have information that we end up getting later. What I would say is that I hope we

don't design anymore future studies for depression in children the way we used to design them.

DR. O'FALLON: But part of the issue is the fact that they weren't designed to assess -- get a definitive answer on efficacy. They were intended to go after safe dose and safety profile. Otherwise, they might have had to go a lot bigger to have gotten the efficacy endpoint.

DR. MURPHY: No, they were supposed to be efficacy files.

DR. ROBERTS: They had to do two adequate and well-controlled. There were placebo-controlled trials because remember when all of these were initially written and they were all written in the same time frame we had no approved products for the treatment of pediatric depression so they all were designed as placebo-controlled trials.

There were two so that they could confirm each other if, indeed, there was a positive effect. They were to adequately demonstrate evidence of efficacy. They all were to have PK. Now, part of the problem is, as I recall from that template, you could

use population pharmacokinetics. You didn't have to do standard pharmacokinetics.

One of the difficulties we are seeing, and I'm sure some of you have seen it, too, is that when you do population pharmacokinetics, you do it as part of your pivotal trial. If they guess wrong on the dose, then you have studied your pivotal trials the wrong dose.

Now, what they typically will try to do, and actually we saw this with buspirone which was studied, there were two trials for generalized anxiety disorder. What they did was they targeted to get the serum level that was effective in the adult population.

Indeed, that's what the patients got. In some cases even higher. It didn't work. So does the drug just not work? Do we need a much higher dose? But they are not going to go back and retry another dose. The other thing is these studies were designed the best we could and powered the best we could but they didn't have to do further because in order to get pediatric exclusivity you didn't have to have a

positive result.

CHAIR CHESNEY: Thank you. We keep learning. I'm sorry you have to keep educating us.

Dr. Gorman.

DR. GORMAN: As we move forward with PREA are we looking at different designs as the drugs are coming through the pipeline for both efficacy? I know we haven't discussed the labeling implications of PREA because it's certainly different than exclusivity. But are the designs different for the pediatric studies as we move forward into PREA than they were under BPCA, or as they are under BPCA? We are trying to get to Dr. Chesney's rigor question.

DR. MURPHY: It shouldn't matter whether they are under PREA or BPCA. They should be the studies you need. If your question is as they come in now that PREA is in effect, would the studies be different? They could be different because, as you know, they can only ask for the studies for the adult indication under PREA. But the trial design -- I guess what I'm trying to say, Dr. Gorman, is the trial design should be the same. Actually we often will

design them for PREA and roll it into a written request.

DR. GORMAN: The question was more in terminology. There is less of a background data source when you are in PREA than there is in BPCA. One of the concerns that I have heard voiced around this table and in other venues is that because the drug has already been shown to be effective in adults that there is sort of somewhat lesser standard for BPCA. Something I have not ascribed to but I've heard this. When you come into PREA the drug has not been approved for adults so is there a different standard as we are moving forward?

DR. MURPHY: Well, it may have been approved for adults but for another indication.

DR. ROBERTS: Now, wait a minute. In PREA the only thing that you can require an assessment on is the indication that's currently being developed or has just been approved. So it would have most likely been studied in the adult population and got approved for that indication. Then the question is is that indication applicable to the pediatric population. If

it is, then studies need to be done.

DR. MURPHY: But they could already have an adult indication. I mean, infectious disease is a gray area. They may have hospital-acquired pneumonia in adults and now they're coming in for community-acquired for adults and that would be applicable to kids so you can ask for community-acquired in kids.

But you may already have all that data out there on adults in the hospital-acquired. I guess the thing is, again, yes there is an issue, as you know, where sometimes we ask for "less" because we are extrapolating the efficacy.

DR. GORMAN: Thank you for reminding about the fact that PREA applies to more than just new molecular entities which is the part that I had forgotten. Thank you.

CHAIR CHESNEY: Well, it's only 6:20. Can we put in another half hour here? A quick question. Are we here again tomorrow morning?

PARTICIPANT: Yes. I won't play musical chairs.

CHAIR CHESNEY: Can we leave the materials

here that we aren't going to use tomorrow to be sent out later? Thank you very much.

DR. MURPHY: Thank you all very much. Very helpful discussion.

DR. ROBERTS: Thank you.

(Whereupon, at 6:23 p.m. the meeting was adjourned.)