U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

MEETING

THURSDAY, NOVEMBER 16, 2006

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The Advisory Committee met in Conference Room 1066, 5630 Fishers Lane, Rockville, Maryland, at 8:00 a.m., Robert Ward, M.D., Acting Chair, presiding.

PRESENT:

ROBERT WARD, M.D., Acting Chair,
Committee Member
CARLOS PENA, Ph.D., M.S., Executive Secretary
AVITAL CNAAN, Ph.D., M.S., Committee Member
ROBERT S. DAUM, M.D., Committee Member
DEBORAH L. DOKKEN, MPA, Committee Member,
Patient-Family Representative
LEON DURE, M.D., Committee Member
ELIZABETH A. GAROFALO, M.D.,
Industry Representative
RICHARD L. GORMAN, M.D.
Pediatric Health Organization Member
MELISSA MARIA HUDSON, M.D., Committee Member
KEITH KOCIS, M.D., M.S., Committee Member
JOHN W.M. MOORE, M.D., M.P.H.,
Committee Member
THOMAS B. NEWMAN, M.D. M.P.H.,
Committee Member
LARRY SASICH, PharmD., FASHP
Voting Consultant, Acting Consumer
Representative
GEOFFREY L. ROSENTHAL, M.D., Ph.D.
Voting Consultant

AGENDA ITEM **PAGE**

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

8:19 a.m.

DR. MURPHY: Despite the weather and everything then, we're ready to go. So Bob and Carlos, I guess, you will get started then and I will come up after that. But one last thing, I did want to make sure the Committee was aware of the new Members. That this, I hope, looks like a smooth prepared process, despite this morning, in which you have received the material, had time to review it and you have a logical presentation and we ask you good questions and you provide excellent advice.

This doesn't occur without a hoard of people and I just wanted to say before we get started today, it does feel like tomorrow already, that this involves an enormous number of people from the Office of Surveillance and Epidemiology who provide you both the Adverse Event Report and then the Use Report from the Office of New Drugs.

Each of these drugs is in a division, you know, a Review Division that is responsible for all of these products. They have been involved in making sure that any information that is relevant to these drugs is also thought about and potentially it will need presentation to the Committee, so the Committee is aware of what else might be going on and the staff of Pediatrics and Maternal Health who are critical in helping us coordinate this across the Agency.

I really wanted to thank all of those people, including the Office of Science, which you have already heard. Dr. Johannessen and Pena are from the Office of Science. And with that last comment, I will turn this back over to Bob.

ACTING CHAIR WARD: Let's see, do you want to go ahead and read the statement for today?

DR. PENA: Thank you and good morning. The following announcement addresses

the issue of conflict of interest in regard to today's discussion of a report by the Agency on Adverse Event Reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act. The Pediatric Advisory Committee will hear and discuss the report by the Agency as mandated in Section 17 of the Best Pharmaceuticals for Children Act.

On Adverse Event Reports for ertapenem, gemcitabine, glimepiride, insulin aspart recombinant, linezolid, meloxicam, ondansetron, oxcarbazepine, ritonavir, rosiglitazone and sirolimus. The Committee will also receive updates to Adverse Event Reports for atorvastatin, citalopram, oseltamivir, oxybutynin and simvastatin, which were requested by the Pediatric Advisory Committee or its predecessor, the Pediatric Subcommittee of the Anti-Infected Drugs Advisory Committee.

When the reports were first presented, the statement is made part of the

record to preclude even the appearance of such at this meeting. Based on submitted agenda for the meeting and all financial interest reported by the Committee participants, it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We note that Dr. Geoffrey Rosenthal is participating as a temporary voting Member and that Dr. Larry Sasich is participating as a temporary voting consumer representative. We also would like to note that Dr. Elizabeth Garofalo has been invited to participate as the non-voting industry

representative acting on behalf of regulated industry. Dr. Garofalo is an industry consultant.

Dr. Richard Gorman is participating as the non-voting Pediatric Health Organization representative acting on behalf of the American Academy of Pediatrics. With respect to all of the participants we ask, in the interest of fairness, that they discuss or they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

ACTING CHAIR WARD: Dr. Rosemary Johann-Liang is going to outline the Committee role and BPAC safety reviews for us, I believe. No? Okay. Introduce?

DR. MURPHY: We changed the agenda on you, too, Bob.

ACTING CHAIR WARD: Oh, that's good. Okay. Okay.

DR. MURPHY: Fitting 16 drugs

required some resorting.

ACTING CHAIR WARD: Right. All right. Well, everybody just go ahead and introduce yourselves. Betsy, do you want to start?

DR. GAROFALO: Sure. My name is Elizabeth Garofalo.

ACTING CHAIR WARD: Turn on the microphone.

DR. GAROFALO: Okay. My name is Elizabeth Garofalo. I'm a pediatric neurologist.

DR. MURPHY: Can you use another mike? The mikes now went dead? Try it now.

DR. GAROFALO: Okay.

ACTING CHAIR WARD: Is it working?

DR. GAROFALO: I think so, this one. I'm Elizabeth Garofalo. I'm a pediatric neurologist. I have more than a dozen years of experience in the pharmaceutical industry. Right now I am a pharmaceutical consultant and I'm the non-voting Member from -- the

representative for the industry.

DR. GORMAN: I'm Rich Gorman. I'm the Pediatric Professional Health Care Organization representative and non-voting, former Chair of the Committee on Drugs. And I'm a pediatrician in private practice in Ellicott City, Maryland.

DR. SASICH: Hi, I'm Larry Sasich. I'm the substitute or the stand-in consumer representative. I'm a faculty member at the Lake Erie COM and School of Pharmacy in Erie, Pennsylvania and I also consult for Public Citizens Health Research Group here in Washington, D.C.

DR. ROSENTHAL: My name is Geoff Rosenthal. I'm a pediatric cardiologist.

ACTING CHAIR WARD: We can't hear you.

DR. ROSENTHAL: My name is Geoff Rosenthal. I'm a pediatric cardiologist from the Cleveland Clinic and an epidemiologist and I'm here as a consultant.

DR. CNAAN: Ah, it works. My name is Avital Cnaan. I was introduced here as the new statistician on the Committee. I direct the biostatistics at Children's Hospital of Philadelphia and have been doing so for about a decade and a half. And I didn't realize I was taking Judy O'Fallon's place.

DR. KOCIS: Good morning. Keith Kocis. I'm a professor of pediatrics at the University of North Carolina in Chapel Hill. My background is in pediatric cardiology and pediatric critical care with an interest in clinical studies, clinical trials.

DR. DURE: I'm Leon Dure. I'm a professor of pediatrics and neurology at the University of Alabama, Birmingham. My interest is in clinical trials and movement disorders.

DR. DAUM: I'm Robert Daum from the University of Chicago. I'm a pediatric infectious disease guy.

DR. HUDSON: I'm Melissa Hudson.

I'm a Member at St. Jude Children's Research Hospital and with the focus in hematological malignancies, particularly lymphoma and long-term follow-up of childhood cancer survivors.

DR. MOORE: I'm John Moore, a pediatric cardiologist from the University of California, San Diego.

DR. PENA: Carlos Pena, Executive Secretary of the Pediatric Advisory Committee.

ACTING CHAIR WARD: I'm Bob Ward, neonatologist and direct the Pediatric Clinical Trials Program at the University of Utah. We're off to an auspicious start here.

MS. DOKKEN: I'm Deborah Dokken. I'm the patient-family representative on the Committee. I have been involved in a number of health care initiatives around family advocacy, including for the last eight years the initiative for pediatric palliative care.

DR. NEWMAN: I'm Tom Newman. I'm a professor of epidemiology and biostatistics in pediatrics, it's not staying on, at UCSF

and a general pediatrician.

DR. MURPHY: Dianne Murphy, Director of Office of Pediatric Therapeutics and we will continue to work on the microphones as we go through this meeting today. And there is a circulating mike and when you are through with your's, please, turn it off, because sometimes that also affects the mikes.

DR. JOHANN-LIANG: Rosemary Johann-Liang. I'm the Deputy Director for the Drug Risk Evaluation, Office of Surveillance and Epidemiology.

DR. MATHIS: I am Lisa Mathis from the Center for Drug Evaluation and Research, Office of New Drugs. I'm an Associate Director for Pediatric and Maternal Health Staff.

DR. MURPHY: Okay. We've got car accidents, red line traffic, weather, is this working? No microphones, but we will forge forward.

ACTING CHAIR WARD: It's on now.

DR. MURPHY: It's all on. Thank you. My task this morning is particularly for the new Members and for some of the Members who have only been here one or two other times is to quickly provide an overview for you, because we are going to be going through 16 products today and we wanted to march through what the process usually is and why we are here.

Okay. This is Section 17 of the Best Pharmaceuticals for Children Act. It is a legislation which fundamentally mandates that any product that is granted pediatric exclusivity will have its adverse events reviewed and brought forth to this Committee for assessment and, if necessary, recommendations.

That is one of the activities which this Committee has been very busy doing over the last couple of years, sometimes meeting two and three times a year, which

might be better than trying to do 16 at one meeting. We'll have to get your feedback on that.

However, where there is also another section of the Best Pharmaceuticals for Children Act which we have not had to ask this Committee to do, but you are authorized to do that, which is dispute resolution for labeling changes and that's why we have throughout every year or so additional training for this Committee and presentations on labeling, risk management, etcetera.

We had presentation at our last meeting on the new physician's labeling. We are going to do another training session today with you and ask you some questions about that. This is a section which we have really not had to use, though we think it has been effective, because fundamentally it says that if the FDA and the sponsor can't come to resolution about this labeling, when they have come to resolution and agreement on everything

else, that it will go forward to this Committee. And usually anybody would sensibly not want to have to take the argument to the public, if we can settle it. So it usually is resolved.

I wanted to quickly review for this Committee the evolution of the process of the safety review. And I have lumped them into two categories: Database issues and reporting practices. A recurrent theme that we have is we don't have a denominator. And this is true. And Dr. Rosemary Johann-Liang is going to review for you the limitations and the strengths of our present Adverse Event Reporting System and some changes that have been made over the last year, as far as additional databases that we have acquired.

We do not have an Active Surveillance Pediatric Program for Adverse Events related to drugs. There is some limited data in that area. And again Dr. Johann-Liang will point those out. We are

working with our Center for Devices and the Office of Safety and Epidemiology is working with them and looking at their MEDS on Active Surveillance Program to see if there are some ways we might work with them and leverage some of that activity.

This Committee has expressed the need for denominator and we understand that need, but again, we will provide you with what we have.

So the second area in which we have heard from the Committee is that you would like us to focus our presentations on the serious adverse events or adverse events we think that might be serious, even though they may not fit the complete FDA definition for serious, which Rosemary will go over with you, and deaths. And we have done that.

So in response to your request, is that we no longer just provide you the top 20, if you will at, you know, what's the frequency of the top 20 adverse events. We do focus on

the deaths and the serious AEs. And if required to provide a better understanding of what is happening in this area, the adverse events are also presented from not only just the one year post-exclusivity, but I know you all will see in the reports, particularly if we don't have enough numbers and the deaths are serious AEs and there is something that might be of interest, we do go back and give you the adverse event since approval for that product.

We also try to make sure that if there is anything going on within the division in the arena of adult information in adverse events that you also hear about that.

The other thing that we have done, in the very beginning, we just gave you the label and our adverse events and you really felt that was not enough. And so we have tried to provide more context for you. And one of the ways that we do that is to give you a review, provide a review of the controlled

trials that were asked for under the exclusivity program. That's done in the presentations that are not abbreviated.

And this is done for two reasons we think. It provides you some idea of what safety signals were we're not seeing during the control trials and it gives you some context of what the benefit might be by looking at this.

The comment I want to make about this is that this plus the medical summary that we also provide you, they are completed facts. We're not going to go back and redo those trials. Certainly, if you want to make comments to us about how you would have done the trial differently or better, we're open to those, but the point of the presentation is really to look at the safety and the efficacy. And if you have suggestions, please, do provide those to us. But they are not the focus of the meeting.

The other things that we have done

relate to how we do these presentations. We have for the last two meetings provided a number of very abbreviated presentations. Normally, the default is a standard, a standard presentation where we go through the exclusivity trials, we go through, you know, the adverse events, the use and then any other information you may need.

When we had looked at this material and see either there is so little use, so little adverse event reporting, we really don't know that it's a useful -- it's a good use of your time for us to go through all of that in a public presentation. And you all have agreed that we can present this in a very abbreviated manner, as long as you receive all of the background material.

So that's why you saw that 8 of the 16 products today are being presented in abbreviated manner. They fell into that category of very little use, very little AEs, no deaths or something that was so confound it

was clear the child died from whatever the underlying disease was.

So the standard, our usual approaches and the in-depths are the ones where it may be anything from just a little more than standard. In other words, we're trying to tell you what's going on within the division and you'll see today we have a couple of those.

And in those situations, we're trying to make sure that the Committee -- there's full transparency, the Committee understands not only what happened with the pediatric adverse events, but also what may be happening elsewhere with these products or the in-depth may be an extensive two day meeting, such as we had with the SSRIs or a one day meeting with the ADHD products.

And then we have only done this one other time, where the Committee requested a follow-up, and that was on the effects of the SSRIs on neonates and we did provide that.

Today we're providing five more follow-ups that the Committee has requested. And those background packages are a little different, because we sometimes elect not to resend you all the old material again.

Okay. Just a quick summary. From June of 2003 to November 2006, this is just for the safety, there have been 10 other meetings or 10 other subjects that we have dealt with under the category of scientific issues. But we have had 10 sessions just to look at safety and there have been 65 drugs that have come forward for review under the first time review. And as I noted today, six follow-ups.

We have had nine products, five of those were SSRIs. Each had in-depth full PAC reviews and there are over 15 categories of drugs that have been reviewed by this Committee. The only thing we can say about drug usage, Rosemary Liang has provided this, is that we can't say much about it except it's

widely variable.

These are the drug categories that products have come to the Committee and you can see it covers the gamut of clinical medicine and the most common product we have here now that has been presented to the Committee has been ecology. And I think that cardiorenal, you can read what the codes are there. This reflects the number of written requests. It's pretty clear that you can get more in the more you ask for.

So today's activities, as has been alluded to, this is the largest number of products we have ever tried to review in one meeting. We welcome your feedback, card to Carlos, please, let him know and me whether you think this has been too much to try to cram into one meeting or you think by doing the abbreviated that it works or it's just too much reading for you all, even though we do abbreviate it. So we would like feedback on that.

There are 11 new products and five follow-ups. Eight of the products have the abbreviated presentations. As a comment though, you received the exact same background materials whether the presentation was abbreviated or not. Some of these products are in the midst of active reviews by the divisions and the approach the Agency is taking is being provided for the Committee.

In these situations, we are often providing information more than we are asking you a question, but we may. In the past, we have asked you to agree with our approach. Do you have any other comments? So you will see some of those today. Some products will have completed the reviews and the Agency will be asking if the Committee is in agreement with returning these products to routine review.

And that, I think, is the end of my comments. And I look forward to your discussion this morning. Rosemary Liang, Carlos, do you want to give a little bit of

introduction for Rosemary, please?

DR. PENA: Dr. Johann-Liang is board-certified in pediatrics and pediatric infectious diseases and is currently the Deputy Director of the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology.

DR. JOHANN-LIANG: Good morning. Okay. There we go. Okay. As Dr. Murphy just discussed, we're going to be really looking at -- you know, our legislative mandate is to look at the one year post-exclusivity period and report to you all in the Committee. But as she also said, often times we really end up looking at the whole post-marketing experience.

And, you know, I'm going to be talking a lot about the limitations of post-marketing surveillance data available, but I want to point out up front, you know, the need for post-marketing data as well and that's because, you know, the limitations of

premarketing clinical trials in the narrow populations are being studied and there are indications of limited duration of study. And, of course, you know, the sample size being small.

And so when we go to post-marketing data what happens is that we start to see safety signals and issues that occur when the drug is exposed to large populations in variable doses and durations and in new populations, including high-risk groups. And the other thing is that even though we may have seen signals in clinical trials, for example, elevated LFTs per say, it's not until it gets to the post-marketing time that we actually see the full development of the clinical presentation of drug-induced hepatitis, hepatonecrosis, etcetera.

The main tool that we use and you have in your reviews for the pediatric adverse events is the FDA Adverse Event Reporting System or AERS. And this captures post-

marketing adverse drug experiences. And I'll go through some of the definitions for you.

This database is voluntary. It's a passive surveillance system and it contains reports that have come in for drugs and therapeutic biologics. It excludes vaccine adverse events, which go to VAERS.

The source of these reports coming into AERS, there are a lot of issues and there is direct reports that come in from consumers and health care professionals and patients and that's the minority of the reports that come in. And there is really no reporting requirement at all for health care providers in this country.

The majority of reports come in through the manufacturer, but again, the requirements for reporting are variable depending on the seriousness, the definitions, and I'll go over this with you, and the expectedness of the adverse event. And we do get reports from foreign sources as well a

domestic U.S.

And because of the source of these reports, there are lots of associated limitations with this data. This is again passive. We're not going out there soliciting or actually getting systemic, systematic reports coming in. This is voluntary. The information is very incomplete and I'll give you an example, many examples. There are lots of reporting biases.

Electronic submissions are coming in more and more and therefore our Adverse Event Reports are going up and up, but there are some good things about it and some not so good things about electronic submissions, too. And all in all, it's the follow-up of the initial report that comes in that we find very difficult to do. So, therefore, the information is not perfect by any means at all. And really it's important for everyone to understand that.

This is an example of a report

that came in and I just sort of blew up the narrative for you. And it basically says this is a 13 year-old patient who developed hepatitis from, you know, a drug, I wiped out to protect innocent, and then it says no further details are included.

And this was an initial report, but there really wasn't a follow-up. And in trying to get the follow-up, this is a case where it was very difficult to do. So this is just an example of sort of the lack of data that sometimes we have to work with. There are times and lots of examples where you get a really long, long narrative that goes through the whole, you know, so you get the other spectrum, end of the spectrum, too.

This is just the numbers. All of this does rise out of, you know, regulation, as defined in Code of Federal Regulations, and these are the areas in the CFR that speak about the regulations of post-market safety reporting, if you wanted to browse through CFR

at some point.

Okay. The definitions for adverse drug experience is any adverse event associated with the use of a drug whether or not considered drug-related, including, and I'm going to just skip over some stuff in the interest of time, unexpected adverse drug experience, and that is any event not listed in the current labeling. So it really turns out to be things are not labeled.

And serious adverse events, this is sometimes confusing, you know, when we think about clinical seriousness and it gets confused with severity of disease. But there is a strict sort of regulatory definition for what constitute an SAE in reporting. And they fall into these categories.

So for example, in the other at the end, this could constitute something where a patient, you know, shows up in the emergency room possibly due to an ADE and needed intervention. That would be considered an SAE

a well.

So, first, what's the positives of this AERS data? Once again, you know, it does include all the drugs and therapeutic biologics that is marketed in the U.S. and it is simple and expensive as compared to other surveillance systems and it is very large and growing. It's up to about 3.5 million reports now and we expect for it to continue to grow, especially with more and more manufacturers doing e-submissions.

It is good for discovery of previously unknown adverse drug events. So adverse events too rare to be seen in trials, adverse events in populations not exposed to drugs and trials, especially pregnant women and possibly young children as well, as you very well know. And what it does is it triggers us. It's a signal generating tool. It triggers us to do further investigation.

We do follow-ups, try to review available data, what's in the literature, what

other possible class effects, etcetera. And we request further studies to study this signal that has been generated through AERS. And as I said before, where the AERS really helps us sometimes is to expand on previous known ADE clinical description. You know, how much broader the breadth of the clinical experience, the seriousness and the severity of ADEs seen in trials.

This is just to show you the size of the database that's continuing to grow and I have modified this from Dr. Kortepeter's slide from a recent talk that she gave and it's 2006 we will probably at the end end up sort of growing too. And when we look at these reports, we try to assess how much of what's being reported to us actually has some relationship to the drug.

We cannot ever attribute direct causality through AERS. Now, it's very important to know we really need randomized controlled trial data to do that. But the

AERS reports does help us, especially if a lot of these categories already in place if there is biologic causability, if there is already signaling an animal preclinical study, if we already have hints, small or large, from clinical trials, there is laboratory help and also with the temporal dechallenge, rechallenge aspects of the case, we can generate a case series to say this is really something that we are concerned about.

Looking at the other side, what are the data limitation? I talked about this already. If that it's a voluntary reporting database and sort of by definition, it's under-reporting. Nobody thinks that AERS isn't over-reporting of adverse events. Even when we talk about stimulated reports due to media attention or etcetera, that's probably still an under estimate of what truly goes on as a drug reaction overlay to what is happening in the big population.

You know, the literature says

possibly 1 to 10 percent of a true incident depending on what adverse events, for what populations, for what diseases. But the nature of the reporting, the bias that occurs is -- you know, it depends on many factors and I have listed them here. How long it has been on the market, what recent regulatory actions, what has come to media attention, different surveillance systems that actually bring this into AERS, etcetera.

And there is variable quality and completeness of reports, as I have talked about already, lots of duplicates in the reports, so you can't -- sometimes grossly you figure out these are the number of this, in the AERS this is the number, but really to try to discern what's going on, you really have to go to hands-on, case review series, which is what we try to do for you for the reviews that are coming from our office.

It's gross estimation of reporting rates of events. This is not incidence rates.

So we give you the numerator of the adverse event counts and then we give you the denominator from the drug use databases that are available to us and we try to sometimes figure out what the reporting rate is. But this spontaneous report numbers cannot be used to determine incidence of adverse events. And that's really important for us to keep in mind.

Again, the limitation is that we cannot attribute causality from AERS data. This is a voluntary system. The main utility is to hypothesis generate.

I have a slide here taken from our Drug Use Specialist Team, Laura Governale's talk recently, and this sort of gives you a very brief overview of drug use databases that are available to us now. And she is supposed to be here, so if you have further questions, you can direct it to her later. But just as a general overview, there have been changes in the last year, some big changes.

You know, for the Members that have been here before you have seen the IMS and the database that was used before. We have sort of converted over all to Verispan now. And for outpatient drug use, we use the Verispan Vector One National or VONA. This really does give us good projections nationally of prescriptions, drug prescriptions and how much prescriptions have gone actually to the patient.

We actually also could look at of those prescriptions, because there is a lot of repeats, right, how many actual patients? And we have gone to a patient level basis and we can do that now, which is very helpful. And also, there is an ability, although this takes a lot of effort from our drug use specialist, to do concurrency analysis. Meaning, we're doing some of this with the ADHD drugs, meaning, if you are on one drug, you know, what other drugs is the patient taking and sort of try to look at trends by age and over

time, etcetera.

And there is also the physician drug and diagnosis audit which is a way to try to assess what are the drugs being used for. So we can't directly link the diagnosis to the prescription, but we do a survey to the physicians to say what are you using the drug for?

For inpatient drug use, we actually can now, before you've been told that we cannot project nationally for inpatient drug use, but with the Premier database, our drug use specialists tell us that they can do that now. You can project nationally for inpatient. What we cannot still do is the Premier pediatric part. It's only 37 centers in the U.S. and we're not at the point where we can project nationally with the pediatrics inpatient drug use.

There are still limitations, the unmet sort of needs. These are all still projections and estimates and for inpatient,

especially, there is no direct link between drug and diagnosis. We do not have good measure of radiological or operating room drug use. Hospital outpatient clinics, especially treatments for chemotherapy or dialysis, and also for over-the-counter drugs, we still have a ways to go.

This is a cartoon taken from Dr. Willy's recent talk. I just wanted to illustrate for you, we may need, especially for you guys in this Committee, to deal with the passive surveillance adverse reporting of AERS, that's the numerator, and then we use the drug utilization data, which is much better now, to estimate the denominator.

But there are other things that we do to try to understand and put the drug safety issue in perspective. But those still have long ways to go. We do have this external health care databases that we have awarded the contract last year, but it is really a study-by-study funding basis now and

that's -- so we need the resources and the money to actually study drug safety question utilizing these contracts that we have in place.

Active surveillance system is very, very at the infancy. We do have some national and regional active surveillance systems in this country and we do try to utilize that, especially look at our, you know, opiod drugs and etcetera, but for the purposes of this Committee in pediatrics, it's really at its infancy as Dr. Murphy had pointed out.

We also try to go in and look at literature to find the actual incidence rates that may be available there. And you will be seeing another sort of a project, ongoing project of another way that we look at adverse events which is to do a meta-analysis of all the clinical trials data available sort of putting it together to see if there is a differential frequency between the drug in

question and whatever the control would be. But this is very resource intensive.

For the ADHD project it took 10, you know, people from our division to work on this to actually put this together.

So moving now to your role today, what we're asking of you is that, you know, you have reviewed the primary materials, which is the one year post-exclusivity AERS reports that was done by our divisional safety evaluator, that focuses in on pediatric AE reports. And I wanted to just reiterate that we are putting emphasis on the serious adverse events and death reports, as per your request.

And then the pediatric drug use data comes from the division of surveillance, research and support, research support, and communication support, that's it. And the drug use specialist will put together the drug use review for you. And you also -- depending on what issue is at hand, you have additional materials for review, material from other

possibly preclinical pediatric exclusivity reviews.

You have drug labeling, possibly literature if applicable and materials from the sponsors and other relevant reviews and information from the Agency. And we ask you to provide feedback and recommendations to us regarding possible changes to labeling, further studies and investigations needed, further surveillance and reports that you want back and other proposed approaches.

And, you know, it really is different depending on the different products and the different types that we need the input from, that we need your input. And again, just to go over, I'm not going to go over this too much again, because Dr. Murphy went through this, is that the abbreviated format, the standard format, there are sometimes when the drugs really need more in-depth review and we have actually devoted whole entire AC meetings on a certain drug or a certain issue.

And we now have actually a new category which is that sometimes you want certain drugs reported back to you, maybe because the first time when we presented, when we had the information, there just wasn't enough reports during that one year and you wanted more or there were certain issues that you wanted a further ongoing follow-up on. Such as with Celexa and Tamiflu discussions today.

Okay. So today's presentations, the abbreviated drugs, RDs, ertapenem, Gemzar, Amaryl, NovoLog, Mobic, for the abbreviated briefly and then the standard presentations are Zyvox, Avandia, Zofran, Norvir, Rapamune and Trileptal and then we will also bring back to you some follow-up information on these five drugs, Ditropan, Lipitor, Zocor, Celexa and Tamiflu and then open up for your discussion and your input.

And I wanted to acknowledge all these folks from, you know, lots and lots of

places throughout the Agency that come together to bring this to you.

ACTING CHAIR WARD: Very good. Is Alan here? You made it.

DR. MURPHY: And, Carlos, do you want? Rosemary's slides will be sent to the Committee. Okay. If you don't have them in front of you, which apparently you don't, we will send them to you. Okay.

DR. PENA: The next speaker is Dr. Alan Shapiro. He is a pediatric infectious disease specialist with a Ph.D. in biochemistry and a medical officer within the Division of Pediatric Drug Development. The Division representative is Dr. Alfred Sorbello, Medical Officer, in the Division of Anti-Infective and Ophthalmology Products.

DR. SHAPIRO: Thank you. I would like to go on to discuss the post-exclusivity adverse event review for linezolid. Linezolid, also known as Zyvox, is an anti-infective, its sponsor is Pfizer, it's

indications are treatment of vancomycin-resistant enterococcus faecium, nosocomial pneumonia caused by Staph aureus, including MRSA, complicated and uncomplicated skin infections, community-acquired pneumonia. It gained market approval in April of 2000 and pediatric exclusivity was granted in February of 2005.

Now, I would like to talk about the drug use trends in the inpatient setting for linezolid. Pediatric patients accounted for, approximately, 1.2 percent of the 27,900 discharge associated with linezolid use in the U.S. from August 2004 to July of 2005. Pediatric discharges associated with linezolid increased from 30 percent from 141 discharges in the six months prior to exclusivity to 184 discharges in the six months following the exclusivity.

Now, to give you a context of our review, we also talk about the exclusivity studies. In linezolid there were several

studies that I'm going to discuss here. The first study was assessment of linezolid pharmacokinetics in full-term and pre-term infants in less than 3 months of age.

The second study was a randomized, blinded comparison of safety and efficacy of oral linezolid versus a cephalosporin for the treatment of skin and skin structure infections in pediatric patients age 5 years to 17 years.

The third study was a randomized, open-label comparison of IV linezolid and oral linezolid and IV vancomycin in suspected Gram-positive infections in pediatric patients from birth to 11 years.

Now, going on to a slightly different tact was a perspective study of vancomycin-resistant enterococcal infections in pediatric patients age birth to 17 years. Also, we did a pharmacokinetics study in pediatric patients aged birth to 11 years with cerebrospinal fluid shunts.

Now, the results of these studies. First, I would like to go over efficacy. The overall results of studies 2 through 4 supported the efficacy of linezolid in treating the following infections in children. One thing I would like to emphasize even though we had all these indications that we did find that there was a highly variable CSF penetration.

In studies 2 and 3, the most common adverse events were diarrhea, fever, vomiting, headache and skin rash. The most common lab abnormalities were reduction in hemoglobin, reduction in platelet counts, white blood cell counts and elevation of alanine aminotransferase.

Also, in Study 4, the study with VRE, the most frequent AEs were gastrointestinal events and the most significant lab abnormalities were decreased platelet count and elevations in ALT and bilirubin. Overall, the safety profile in

children is similar to that in adults and is consistent with the known safety database and current labeling.

Now, I would like to go over the pharmacokinetics results. Systemic exposure to linezolid varied as a function of age. There was rapid clearance in patients greater than 1 one week old to 11 years, hence, there is a need for every eight hour dosing. The mean clearance in adolescents approached that in adults, hence, there was a need for every 12 hour dosing. But one thing we did notice was reduced clearance in neonates less than 34 weeks of gestation and less than 7 days post-natal age, hence, the need for every 12 hour dosing.

Due to the wide variability in clearance of linezolid in pediatric patients, there is a possibility of subtherapeutic levels with the recommended dosing regimens. One concern is in treatment of infections with a high MIC of the infecting organism. This is

especially true in the context of severe life threatening infections. Thus, the recommended dose of linezolid depends on the weight, the age of the patient and the clinical indication.

Now, labeling changes resulting from exclusivity studies. There were pediatric labeling for the following indications listed, including nosocomial pneumonia, community-acquired pneumonia, vancomycin-resistant enterococcus faecium infections, complicated skin and skin structure infections, uncomplicated skin and skin structure infections.

Now, also, there was pharmacokinetics data in pediatric patients with ventriculoperitoneal shunts. They did find variable cerebrospinal fluid concentrations and the therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, I would like to emphasize that the use of linezolid

for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

Okay. Now, to go on to the Adverse Events Report since marketing approval. In all ages, there were 1,846 Adverse Event Reports of which 1,418 were serious and there were 168 deaths. Now, in the pediatric age range, there were 50 reports of which 40 were serious and there were two deaths.

Now, going on to the reports in the 13 months in the post-exclusivity period. For all ages, there were 395 reports of which 377 were serious and there were 61 deaths. Now, in the pediatric age range, there were 18 reports of which 16 were serious and there was one death.

One thing that's important with linezolid is that many of these adverse events that I'm going to talk about are in the label, so I want to make you familiar with

linezolid's label, so I'm going to go over some significant aspects of it.

The first is the warning section. There is a hematologic. We do find myelosuppression, also pseudomembranous colitis, which is a standard warning for all antibacterials.

And the safety concerns in the precaution section include lactic acidosis, serotonin syndrome, drug interaction with adrenergic agents, including phenylpropanolamine and pseudoephedrine, and serotonin agents, including antidepressants such as SSRIs. There are also food-drug interaction with foods containing tyramine. Also, peripheral and optic neuropathy usually with the use of greater than 28 days.

Now, in the post-marketing reports there were myelosuppression, peripheral and optic neuropathy and lactic acidosis and serotonin syndrome. Now, pediatric deaths since marketing approval, there were three. I

want to emphasize that. In your report, you have two of them mentioned. The third one came after our safety cutoff date of March 11, 2006.

Now, the first death was in a 2 year-old with severe thermal burns with vancomycin-resistant enterococcus who had a poor prognosis when starting antibacterial therapy. The second was in a patient, a 3 year-old, with graft versus host disease, acute respiratory distress syndrome, renal failure, GI candidiasis and staphylococcal infections. This patient was on multiple medications, including cyclosporin, other antibacterials, micafungin and acyclovir.

And the third case, as I mentioned, that is not in your paperwork is a 12 month-old patient treated for MRSA sepsis and endocarditis, which we have no additional data available.

Now, the serious pediatric adverse events in the post-exclusivity period, there

were 15 unduplicated pediatric reports for patients on linezolid. There were five neurologic adverse events, which were listed below, which are all labeled. There were six cardiac adverse events, which were unlabeled, which include tachycardia, irregular heartbeat and chest pain, arrhythmia and abnormal EKG. There was one in the gastrointestinal/ hematological category and three in the metabolic. All of the gastrointestinal/ hematologic and metabolic were labeled.

Now, going on to the cardiac adverse events, I would like to discuss in a little more detail. In the cases of tachycardia, we had a 2 year-old male treated for enterococcal urinary tract infection with tachycardia, which additional history is not available.

We also had a 16 year-old male with osteomyelitis who experienced persistent tachycardia which normalized two to three days after stopping therapy. This patient had

consumed a large amount of beef jerkey and there is an interaction between tyramine and the weak monoamine oxidase inhibition of linezolid.

There was also a 6 year-old female with MRSA catheter infection with sepsis who developed tachycardia of 220, hypertension and rapid breathing within the first few minutes of initial infusion. This patient recovered after treatment was stopped.

Now, for a case of chest pressure and irregular heartbeat, we have a 9 year-old female with cystic fibrosis on multiple other antibiotics for upper respiratory infection. After the first dose of linezolid, there was a crushing chest pressure and irregular heartbeat. The irregular heartbeat and chest discomfort persisted after linezolid was stopped.

There was also a case of abnormal electrocardiogram. This was a 10 year-old female with MRSA pneumonia who developed

hypokalemia and an abnormal electrocardiogram on the sixth day of therapy. Hypokalemia and the abnormal EKG improved following discontinuation of linezolid. This patient was also on other medications.

Now, also to discuss the case of cardiac arrhythmia. There was a 15 year-old male who experienced chest discomfort and AV disassociation and a junctional rhythm. This arrhythmia persisted despite reduction of linezolid dose and resolved two days after linezolid was stopped. This patient though had a history of premature atrial contractions with junctional escape beats and wandering atrial pacemaker.

Now, to summarize. The Office of Surveillance and Epidemiology will conduct a full review of cases of cardiac arrhythmias reported with linezolid in patients of all ages. We will provide the Committee with the results of this OSE review. This completes the one year post-exclusivity Adverse Event

Reporting as mandated by BPCA.

FDA recommends routine monitoring of adverse events for linezolid in all populations. Does the Advisory Committee concur?

I would like to acknowledge the following individuals who have helped in the preparation of my presentation. Thank you.

ACTING CHAIR WARD: Alan, thanks for a very thorough presentation. Let me just ask the Committee if they concur with the recommendations that have been made, noting that cardiac events will be brought back to the Committee, or if they want to open this to discussion. Bob?

DR. DAUM: First, we'll talk about nothing happening?

ACTING CHAIR WARD: Right.

DR. DAUM: So the first, the question is in terms of developing resistance to the nasal, an antibiotic resistance during therapy. Is that within or outside the

purview of this review?

DR. SHAPIRO: If there are cases of failed therapy, that does come under an adverse event. It depends on the clinician to report it to us. But definitely failure of therapy does fall in that spectrum.

DR. DAUM: Well, then what's the proper thing to do, because I could make a comment about the issue or I could just propose that this be something that you monitor as well in the coming year. Advise me here.

DR. JOHANN-LIANG: In AERS, we get reports in for lack of efficacy, but it's really not a good database, I think, to look at antibiotic resistance, for example. We may get occasional examples in saying, you know, this drug was resistant and therefore it didn't work, etcetera. But again, it's not considered really an individual adverse event drug experience that I can -- it doesn't mean that that's something that we shouldn't be

looking at.

It is a safety issue and a global safety issue. But I just think that the database that we have for AERS is not the appropriate tool for that kind of question.

DR. DAUM: So the question then is what is? How should we proceed with that?

DR. MURPHY: Our infectious disease societies would take this on as an issue, you know, something along that line.

DR. DAUM: Beyond the scope of what we're doing here.

DR. MURPHY: Yes. I think that to get to that issue, you really need a prospective trial and I don't think we could get it out of our AERS database, Bob.

DR. DAUM: Okay. Well, I might just comment then that there is resistance being seen now. It is known to the company and known to many clinicians and it appears to be related to duration of therapy, so that the longer you use the drug and the organisms able

to survive because it's sequestered medically during that time, resistance may occur.

The number of isolates are still very small and there's no reason for alarm, but it's a prolonged use kind of thing. Also, the hematologic toxicity that you talked about, I believe, is also related to duration of use. And so if you're going to collect additional data for even in the cardiology sphere, noting something about duration of use would be a very helpful kind of thing. It looks like the more you use it, the more these things occur.

DR. SHAPIRO: I would like to add one thing. In the label, there is a warning about optic and peripheral neuropathy in use longer than four weeks and that actually, as a clinician, I also practice infectious diseases, that always worries me. Whenever I get to the four week mark on a patient on linezolid, I always look at either stopping or getting ophthalmology exams.

So I think there is also that other limitation and it's prolonged use, it's those side effects. And some of the ophthalmology even though you have an ophthalmologist check their eyes, that does not always predict that you are going to develop an optic neuropathy or not. So I think there is a built in concern already in prolonged therapy for this drug.

DR. JOHANN-LIANG: I wanted to add a couple of things. What you can recommend maybe for the purposes of understanding this pediatric safety issue and the resistance is a safety issue, further is to request that perhaps a dialogue between the Review Division and the sponsor take place to see if there are further prospective investigations that can be done to address this.

And then, secondly, regarding infectious disease and antibiotic-resistance, there is an interagency task force called The Get Smart Program that is trying to look at

antibiotic-resistance from a, you know, broad, multiple federal agency level.

And so it is mainly geared towards outpatient use, but there are other ways that perhaps we can look at antibiotic-resistance, but it wouldn't be in the purview of post-marketing spontaneous data. It really needs to -- we need to engage the sponsor and other stakeholders to examine this issue. Okay.

ACTING CHAIR WARD: Good. Rosemary, if, for example, Dr. Daum at University of Chicago establishes a certain rate of resistance and it's confirmed in a couple of other places around the country and it's published, would that be information that could later be placed in the label through negotiations between the Agency and the sponsor?

DR. SORBELLO: Let me just make a few comments. I think certainly the Review Division -- let me make a few comments. Certainly, the Review Division would be

interested in acquiring more information about resistance.

Frequently, we have to rely on what is published in the literature, whether it's case reports, case series or other studies that have been published to give ourselves an idea of what is happening. We'll certainly be interested in that.

I think the other thing to keep in mind with some of the AERS reports is that the use of the drug, and it's frequently off-label, and it's of more prolonged duration that's within the label, the label talks about durations up to 28 days and some of these, they are quite extensively long periods of time that patients have been on the drugs.

And we're also limited by the quality of the reports themselves. We don't often get information as far as other concomitant meds or even concurrent illnesses, but when you look at the age group, a number of them are usually older patients, which

would be at a higher risk to having other medical problems and other issues going on. So it does tend to compound trying to sort out some of the safety issue with linezolid.

DR. MURPHY: I guess to answer your question, Bob, if anybody has a trial which has important information, they can submit it to the sponsor, to the Agency, publish it in the literature. You know, I mean, a multi-prong information approach and submission for review would be the way to go.

ACTING CHAIR WARD: Well, I think what we're hearing, there is an avenue to inform the prescribers about changes in resistance patterns.

DR. DAUM: We clearly need more information and I think we should try and get that information via the appropriate routes that we have been discussing.

PARTICIPANT: We need duct tape or something on these connections.

DR. NEWMAN: To answer, the

studies done for exclusivity are a done deal, but I have to say to see in Study No. 2 that this big gun drug about -- we're worried about resistance developing. And it costs $60 a pill being compared to a first generation cephalosporin for uncomplicated skin infections in a randomized double-blind trial makes no sense to me at all to be able to show that it's not inferior to something that costs 100 times less and is safer.

Does anyone have any idea what the thinking was of having that be one of the studies for exclusivity?

DR. MURPHY: Tom, I think that the trials that are designed, at the time that they are designed for exclusivity, have to be consistent with whatever their -- with two things. First, I should say, with what the division thinks is a public health need and then the second is it has to be consistent with what they think is the best approach that they have been using.

Now, that doesn't mean that we don't change over time and it may be that if they had to do that study now, they would not do it that way, because we have changed how we do studies as we get data in. What you're saying is you don't think then back in whatever, 2000 -- when was it, Alan, that this was studied?

DR. SHAPIRO: I think, I can check with Alfred, but I think they go back to about 2000 sounds right.

DR. MURPHY: Yes, 2000, right. So six years ago when the trial was designed, that that was consistent with the approach that they were taking. And, as I said, Dr. Sorbello and others would be in the -- in the Anti-Infective Division would be glad to hear your thoughts.

DR. NEWMAN: So my thought is the study that is being done for uncomplicated skin infections compared to a first generation cephalosporin that seems -- it makes no sense

to me at all.

DR. MURPHY: Noted.

DR. NEWMAN: I'm just asking.

ACTING CHAIR WARD: Dr. Sasich?

DR. SASICH: Thanks. Also a comment. Is this working? I will speak loudly then. Also on Study No. 2 or 065, if you take a look at the labeling in pediatric studies, it mentions a comparison trial between Zyvox and cephalosporin. One isn't -- the cephalosporin was used as a comparators actually means it seems like that would be a useful piece of information for prescribers.

Then I have a couple of other questions also. It seems to be inconsistent policy within the FDA when we see these studies that if you go to review documents and you go to the website, you can see comparative trials, and then you go to the labels and comparators aren't named. I could have missed cefadroxil in the pediatric trial section. It's an extremely long paragraph.

DR. MURPHY: That's a labeling issue that is negotiated between the division and the sponsor. I can tell you that usually, and if anybody from that division would like to correct me, I will be glad to stand corrected, they tried not to label the comparator, but sometimes they do. There have been times when the comparator is put in the label.

DR. SASICH: I think it would be useful for clinicians to know what the comparator was. A couple of other questions.

On the three cases of neuropathy, do we know the duration of treatment of those patients? I think we had one optic and two peripheral.

DR. SHAPIRO: See, one was a 6 year-old. I have it for eight months of therapy on the optic neuropathy, which is well beyond the recommended time.

DR. SASICH: Yes.

DR. SHAPIRO: And the peripheral

neuropathy I see about four weeks of oral linezolid, so just to get you on those cases there. I have the two in front of me.

DR. SASICH: So they were right at the edge of the labeling. The gentleman over at the other side of the room mentioned a lot of off-labeled use that -- of the drug greater than 28 days.

Is it worthwhile considering strengthening the 28 day warning or to think about it if we're seeing a lot of off-labeled use?

DR. SORBELLO: I think certainly we would like -- you know, we would definitely consider that type of issue, because the Agency has warned in the past --

DR. SASICH: A number --

DR. SORBELLO: -- over off-label, off-label.

DR. SASICH: Sorry.

DR. SORBELLO: The Agency has warned in labels in the past over off-labeled

use, particularly when it was harmful.

DR. SASICH: Yes. I mean, it certainly may be something to consider, because when you look at the cases that you see through AERS, a number of them are patients with bone infections, serious staph infections that require prolonged durations beyond four weeks.

DR. SORBELLO: Thank you.

DR. MURPHY: So should we take that as a recommendation then? Is that what you're suggesting, that we go back and look at AERS and see where we have prolonged use and off-label use as far as adverse events?

DR. SASICH: I think it's entirely worthwhile, particularly if it was a skin and soft tissue infection or some other condition for which there was another approved antibiotic that wasn't without the adverse events.

ACTING CHAIR WARD: Okay. Lisa?

DR. MATHIS: I do want to just

make it really clear that it's very important for the Committee to recognize the difference between FDA labeling and the practice of medicine. The FDA does not regulate the practice of medicine and we actually expect physicians to be able to use their judgment and to be able to look at an individual patient and treat that individual patient.

So while we'll go back and look at the data, I think it's always really important to remember that we don't want to fill the labeling so full of individual cases that it makes it very difficult for a physician to be able to use that medication as they feel they need to for an individual patient.

So, again, the off-label usage I'm sure will be considered, but we have to be very careful that we don't get into the business of regulating the practice of medicine.

DR. SASICH: Well, I don't see how warning regulates the practice of medicine.

It's simply warning. It's reflecting what we know.

DR. MATHIS: It just has to be based on the information, so I think --

DR. SASICH: Right.

DR. MATHIS: Yes.

DR. MURPHY: So I think what we hear, just to wrap this up, is that there is a concern that we know we have a problem with prolonged use and we want to look at that amount of prolonged use, and then we want to look at our adverse events and see in those cases is it a matter of prolonged uses causing them.

And then ask the question if it is, if it isn't, if that doesn't -- if those prolonged use cases are not having adverse events, which would -- actually, if it's not the usual adverse events you associate with prolonged use, resistance, optic issues, then it's going to be hard to put additional warnings.

If, however, that additional prolonged use seems to be associated with some of the things that we think would result from that, then we would ask to look at restrengthening. You are asking to look at strengthening the labeling in that area.

ACTING CHAIR WARD: Dr. Cnaan, one last comment.

DR. CNAAN: I'm trying to understand the recommendation from the FDA. The recommendation is to further review more in-depth the cases that we are seeing and then not to come back with the same review for, say, a period of another year.

And the reason I'm asking that is if I'm looking at the slide that summarized everything, it should a comparable number of the cardiac cases and the neurologic cases within this one year with the neurologic being labeled, the cardiac being not labeled. In the absence of any denominator, the only thing I could compare the cardiac is to the

neurologic.

It seems to me that the logical approach would be to come back in a year, if we're still seeing the same pattern to say, well, there is something there. But I'm not sure that that is what the proposal is, because I don't entirely yet understand the language.

ACTING CHAIR WARD: Alan, do you want to respond to that?

DR. SHAPIRO: Well, the thing was with the cardiac adverse events, when we did the review, it highlighted to us. So what we have is OSE is now in the process of reviewing that and that review is in process, and that we had mentioned that we were going to report back to you what that review says.

Right now, it's too early for us to make a definition, but they are trying to get an idea of the scope of the cases there and it's hard to say when you see these cases until you take a further look of how

significant they are, so we're still in that process.

DR. DAUM: Just one comment in response to Dr. Mathis and then one other comment about just the table.

I don't think the issue is regulating the practice of medicine. I think the issue is informing practitioners that there may be problems with prolonged use both in safety and efficacy. And so I think the educational part is what we need to be a bit proactive in.

And the second point is that I don't know if everyone at the table realizes it, but MRSA infections in the community are epidemic now in most of our country. And this is one of the few drugs that actually is sort of helpful in the beyond MRSA kind of sense, and so that it becomes very, very important for us to understand all the issues with safety and all the issues with resistance, because pressure is going to be put on this

drug for increased use both on-label and off-label.

DR. SHAPIRO: I'm sorry. I would concur. I would -- you know, right now it's basically, as all of us know, it's the insurers that basically regulate that use of linezolid and, for the most part, you have to show that the patient does not tolerate or has a problem with vancomycin before I can get most insurances to approve it there, and so it's one of these things.

Yes, it's the next line. If a patient needs, you know, therapy and you're concerned that they are not tolerating the vancomycin, linezolid is an option.

The other thing is that people like to say, oh, it's convenient. You don't have to have the patient on IV therapy. You can put them on the oral form, but I think for most of us we're kind of reluctant, because we are worried about resistance if it starts being used that way.

DR. KOCIS: I just want to come and agree completely with the need for coming back with a report on the cardiac toxicities, but I wonder whether it would be prudent to at least mention the cardiac side effects mostly because of the severity of them, heart plate, heart block, hypertension and tachycardia which, in my mind, reach a threshold based on severity that would again lead me to want to warn not create hysteria or change labeling or things like this time.

But so the question really is should we make a comment at this point while we're studying further or is it best to wait to get further data before making comment?

DR. MURPHY: I would posit that usually if the division, meaning the Review Division, has had enough adverse events, and again this is hypothesis setting because they are always confounded, but if there is enough, as you're going to hear about Tamiflu where we still don't know, I mean, because the cases

can have -- they will decide to provide additional education in the label to the physician. This is something else, you know, we think you should think about. We don't know if it causes this problem or not.

I think what they are trying to tell you right now is that with the cases they have, even though the numbers are the same for Adverse Event Reporting, there were other things that went on in the trials that caused them to have those other things in the label previously.

So this is post-marketing Adverse Event Reporting. They really are asking to have additional time, which is what happened again, you know, as you heard with some other products where we think we need to get more cases, see if we get better information.

And the reason for doing that is if you can have better clarity. The more diffuse something is, the less useful it is to the practitioners. The more information you

can get, the more clarity you can get on it, the more useful you can hopefully provide that information.

And that is what I think I understand is what is happening with both OSE and the division, is that they would -- they just don't want to be premature at this point and they want to have some additional data, but they will come back and present this to the Committee.

ACTING CHAIR WARD: Right. Any other discussion? Okay. Let's -- yes, Rosemary? That's fine.

DR. JOHANN-LIANG: I just wanted to quickly respond to Dr. Newman's comment about studying these big gun antibiotics in the face of resistance for things like, you know, mainly sort of uncomplicated, self-resolving diseases like uncomplicated skin indication, sinusitis indication, you know, AECBS.

I mean, there is a lot of

discussion going on in the Agency for us to try to do better that is not just a non-inferiority act of control, you know, not understanding even the margin of efficacy anymore, but really trying to scientifically derive what the margin of benefit is and then go on from there, and to possibly really start doing placebo-controlled trials and trials that make sense in the sense of what is that drug going to be used for in the face of all the resistance that is happening.

So your point is very well-taken and thank you.

ACTING CHAIR WARD: Very good. Thank you. Lisa, let's go to rosiglitazone.

DR. PENA: The next speaker is Dr. Lisa Mathis. Dr. Mathis is the Associate Director for the Pediatric and Maternal Health Staff in the immediate office of the Office of New Drugs in CDER. Dr. Mathis is a board-certified pediatrician and Associate Professor of Pediatrics at the Uniformed Services

University of the Health Sciences.

The division representative here is Dr. Joanna Zawadzki. She is a medical officer within the Division of Metabolism and Endocrinology Products.

DR. MATHIS: Hi, and you will see on the slide that it says Dr. Hari Cheryl Sachs and she did actually prepare all these slides, but is taking care of patients today, so I'm going to be presenting them for her. Thanks. All right. Okay. Okay.

This is just an outline for the standard review, but since you have already seen one, you know what is already included in them. That includes background information, drug use trends, a description of the exclusivity studies, the labeling changes that occurred as a result of the exclusivity trials, additional relevant safety labeling and post-marketing adverse events.

So I'm going to start with Avandia or rosiglitazone, which is an oral

hypoglycemic agent from GlaxoSmithKline. It was originally approved for marketing in 1999 and pediatric exclusivity was granted December 9, 2004. I should take a minute to mention that there are no pediatric approvals for this drug, no indications.

The current indication for rosiglitazone is adjunct to diet and exercise to improve glycemic control in type II diabetes melitis in adults. There are also other related combination products that contain rosiglitazone. That is Avandamet and Avandaryl.

The dispensed prescriptions for Avandia and Avandamet have been increasing in the last three years with Avandia and Avandamet together accounting for greater than 55 percent of the total thiazolinediones dispensed during the one year post-exclusivity.

Pediatric patients account for less than $1/10^{th}$ of a percent of those who

received prescriptions and a majority of these patients are between the ages of 12 and 16 years with the only diagnosis being diabetes melitis. The reviews from the exclusivity studies are posted on the FDA website. This is where you can find it. And, now, I'm going to describe those studies conducted for exclusivity.

There was a safety and efficacy trial of which a subset of those patients underwent population PK. From that population PK study, there were 96 adolescents aged 10 to 17 years of age and the results were that the systemic exposures were similar to estimates from adult studies. This information was incorporated into labeling.

For the efficacy trial, this was a 24 week, multi-center, randomized, active-controlled trial of 200 adolescents with type II diabetes. There were treatment naive, as well as treatment experienced patients with a HbA1c of 7.1 to 10 who had failed diet and

exercise alone and had no evidence of type I diabetes.

The primary endpoint was the change from baseline in both the fasting glucose level, as well as the HbA1c. The secondary endpoint was a non-inferiority between the comparator, metformin, and rosiglitazone.

The Review Division actually ended up looking at both of these endpoints as primary because of the fact that the difference between groups was not felt to be sufficient enough to determine whether this drug was efficacious.

The studies were unable to detect a meaningful difference in HbA1c between the treatment groups. There was also increased weight gain in those patients who were on rosiglitazone when compared to metformin and there were labeling changes to reflect this.

There were no deaths in these trials, but there were serious adverse events.

There was one for rosiglitazone, which was mild DKA, which required insulin rescue, and six for metformin to include hyperglycemia, suicidal ideation, status asthmaticus and menorrhagia.

The adverse events that resulted in withdrawal from the study included six for rosiglitazone, hyperglycemia, bronchitis, gastroenteritis, rectal hemorrhage and facial and hand edema. Some of those occurred all in one patient. And seven for metformin, hypoglycemia, hyperglycemia, elevated LFTs and nausea and vomiting. Oops, sorry.

For the labeling changes that resulted from the exclusivity studies, we have in the pediatric clinical pharmacology section that the PK findings are consistent with those seen in adults. Under the precaution section of labeling, we have clinical trials described under the pediatric use subsection and also a precaution about weight gain.

Under the adverse reaction

section, we have adverse events described that occurred in the trial. We also have -- this is existing labeling. I'm sorry, this was not as a result of the pediatric exclusivity trials. So we do have a contraindication for hypersensitivity.

There is a warning about cardiac failure and other cardiac events, as well as fluid retention. There are precautions regarding hypoglycemia, edema, weight gain, decreased hemoglobin and hematocrit, ovulation and elevation in LFTs, potential liver failure and a need to monitor liver function tests.

Rosiglitazone is a Pregnancy Category C and under the dosage and administration section of labeling, it says to use the lowest dose and to monitor for fluid retention.

Now, turning to adverse events since market approval in 1999. For the raw counts, all ages, all reports, there were 9,072. 3,841 were serious with 365 deaths.

In the pediatric population, there were 14 reports with 10 being serious and one being a death.

The adverse events prior to granting of exclusivity were 12 and after, two, so you can see that the adverse event rate remains about the same for this drug before and after exclusivity.

For the fatal serious adverse events since approval, this was a 6 month-old male product of a premature gestation, multiple birth gestation who died from respiratory failure secondary to ascites from liver failure and biliary artesian.

This infant was exposed in utero to metformin, clomiphene and rosiglitazone. Again, this was a premature birth with multiple medical problems and the twin B survived and is actually described later under adverse events.

The non-fatal adverse events prior to exclusivity included six accidental

ingestions, three in utero exposures to include twin B from the pregnancy previously mentioned and two liver enzyme abnormalities.

The adverse events since exclusivity was granted for all ages, all reports, 1,389. 679 of those were serious with 50 deaths. In the pediatric population there were two reports with zero serious and zero deaths.

So, in summary, labeling was updated after exclusivity studies describing the pharmacokinetics and clinical studies and to reflect that data are insufficient to recommend the use in the pediatric population. Adverse events were incorporated into labeling and include weight gain, hyperglycemia and DKA risk.

There are no new pediatric adverse events identified during the one year post-exclusivity period. This completes the one year post-exclusivity Adverse Event Reporting as mandated by BPCA, and the FDA recommends

the routine monitoring of rosiglitazone for adverse events in all populations. Does the Advisory Committee concur?

ACTING CHAIR WARD: Dr. Sasich?

DR. SASICH: Just another labeling issue. In taking a look at the information for patients, let me -- sorry, I don't have it open.

The patient information portion of the professional product labeling says that the safety and efficacy of Avandia has not been established in children under 18 years of age, and I think that is an enormously unclear statement and I think that is the type of statement that used to appear in the professional product labeling and has finally been resolved to name comparators, and I think this is the other example that I was thinking about.

The comparator is named in the professional portion of the labeling for this drug, but it's not in the patient information

section, even though patients probably never see the patient information section, because I doubt if pharmacists actually ever pass them out to anyone.

DR. MATHIS: Yes. You know, this, that patient information section, is actually for the physician, the information that the physician should be providing to their patient as they are prescribing drugs. Are you looking under the precautions?

DR. SASICH: No, this is the portion. This is the portion of the label that is written specifically for the patient with the intentions on the part of the sponsor or the Agency that patients will see this information. The Agency can request it or the sponsor can voluntarily do it, but it's written in non-technical language for --

DR. MATHIS: Okay. Okay.

DR. SASICH: That is the part that is hooked onto the end of the professional label.

DR. MATHIS: Got it. Okay. Yes. I'm sorry.

DR. ZAWADZKI: I think you may be looking at an old version of the prescribing information.

DR. MURPHY: Which we sent you.

DR. SASICH: No, I am looking at the patient information. This is in the label that the Agency sent around. It's at the very end of the professional product labeling. It's numbered page 27.

DR. ZAWADZKI: Thank you.

ACTING CHAIR WARD: Just above the what is type II diabetes.

DR. SASICH: It's the last page --

DR. ZAWADZKI: The last part.

DR. SASICH: -- of the label that you distributed to the Committee.

DR. ZAWADZKI: Oh, okay. You're looking at the comment that safety and efficacy have not been established in children under 18 years of age?

DR. SASICH: Yes, and the material that was written for patients with someone's intention that it be distributed to patients.

DR. ZAWADZKI: That is a good point. Can you tell me how you would rephrase it?

DR. SASICH: Some way that I would communicate to the reader that the drug actually has been tested. Reading this statement, it could be, well, it hasn't been studied so maybe it's worth a chance. We'll try the drug.

If it has been studied compared to another drug, the Agency's opinion that it doesn't rise to the level of safety and effectiveness for type II diabetes. It has got to say that. Nobody can do anything with this statement.

DR. ZAWADZKI: Sure.

DR. MURPHY: So it's in the labeling, other part, not the part that's at the bottom for the patient. We had that

information. So what you're saying is we need to put something in that latter part that says we all agree and we're getting away from that, and what you're saying is that you're getting there, FDA, but you missed.

And so what you're suggesting is that in the patient part of the end of the label, we at minimum say, please, see pediatric statement about or something that has been -- this has been studied. Please, see other information.

DR. SASICH: Remember, this is supposed to be given to patients.

DR. MURPHY: Right.

DR. SASICH: And so patients normally don't have --

DR. MURPHY: They won't get the whole rest of the label is what you're saying.

DR. SASICH: Right.

DR. MURPHY: So we need to --

DR. SASICH: And so it needs to be clear in --

DR. MURPHY: Right.

DR. SASICH: -- the information that you distribute to patients.

DR. MURPHY: Yes.

DR. SASICH: Or to patients' parents in this case.

DR. MURPHY: Yes.

ACTING CHAIR WARD: Yes, I think the point is that this is a very clear section back in the main label.

DR. MURPHY: Right, right.

ACTING CHAIR WARD: And that the wording probably needs to be changed a little bit for the public, but it really communicates effectively.

DR. MATHIS: I agree and I think it's funny. You're right. We have come to the realization that that statement in physician labeling is absolutely not helpful and that it's much better to describe exactly what we know, and it would be nice to translate that into more common language for

the patients as well.

DR. SASICH: If the physicians are confused, imagine how the patients --

DR. MATHIS: Yes.

ACTING CHAIR WARD: So can we make that general recommendation about that issue about labeling, that we move some of that information, where it's possible, into the patient section.

DR. ZAWADZKI: I think one of the limitations with the patient labeling is that it is very brief and in order to communicate the complexity of this issue in the prescribing information, it really is a fairly extended section actually with a description of the actual study and the comment, the conclusion that the data are not sufficient for an indication.

That is very difficult. You know, it sounds -- I think it's an excellent recommendation and looking at it from a new perspective now, I totally agree, but I think

the translation will be a challenge.

ACTING CHAIR WARD: We wouldn't minimize that. All right. Rich?

DR. GORMAN: The drug has been studied in children and found not to work.

DR. MATHIS: Very good.

ACTING CHAIR WARD: Okay. If there are no other issues, does anybody object to moving on to the next discussion? Okay. The Zofran ondansetron will be presented by Dr. Collins.

DR. PENA: Dr. Collins is a board-certified pediatrician, an assistant professor of pediatrics at the Uniformed Services University of the Health Sciences. The division representative here with us is Dr. Joyce Korvick, Division Director, Division of Gastroenterology Products.

DR. COLLINS: Good morning. I am pleased to be able to present to you the one year post-exclusivity adverse event review for ondansetron.

Zofran or ondansetron hydrochloride is a serotonin HT_3 receptor antagonist. Although its mechanism of action is not fully characterized, ondansetron's binding to serotonin receptors is thought to block the stimulation of vagal afferents that initiate the vomiting reflex. The drug sponsor is GlaxoSmithKline and original market approval occurred on January 4, 1991 and pediatric exclusivity was granted on December 1, 2004.

Prior to the pediatric exclusivity studies, ondansetron was indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin, and the prevention of postoperative nausea and/or vomiting. And for the remainder of this presentation, I will abbreviate chemotherapy-induced nausea and vomiting as CINV and postoperative nausea and vomiting as PONV.

The next three slides provide information about the use of ondansetron in outpatient and inpatient settings. In the outpatient setting, 1.6 million ondansetron prescriptions were dispensed for all age groups during the 12 month post-exclusivity period. 6.6 percent of these prescriptions were for the pediatric population.

There was an 11 percent increase in outpatient prescriptions for all age groups between the 12 month pre and post-exclusivity period with a 39 percent increase for the pediatric population.

Ob/gyn was the most frequent prescriber specialty during the 12 month post-exclusivity period at 23 percent compared to pediatrics at 4 percent. Malignant neoplasm of the brain was the diagnosis most frequently associated with ondansetron use in the pediatric population at 18 percent.

In the inpatient setting, per a database of 450 acute care hospitals, there

were, approximately, 390,000 in-patient discharges associated with ondansetron use for all age groups during the six month post-exclusivity period. 3.2 percent of these drug-associated discharges were in the pediatric population.

There was a 2.7 decrease in discharges associated with ondansetron use for all age groups between the pre and post-exclusivity periods and a 7.3 percent decrease in the pediatric population.

Prior to the FDA's issuance of a written request for pediatric studies, there already was drug labeling for older children. Thus, the written request sought studies of younger populations for which there were no data.

Three trials contributed to the pediatric exclusivity studies. Number one was a PONV pharmacokinetics or PK study in 1 month to 2 year-olds in which 51 pediatric surgical patients utilized ondansetron

prophylactically.

Number two was a PONV efficacy and safety study in 1 month to 2 year-olds in which 670 pediatric surgical patients utilized ondansetron or placebo prophylactically, and number three was a CINV efficacy and safety study in 6 month to 4 year-olds in which 76 pediatric cancer patients receiving moderately or highly emetogenic chemotherapy utilized ondansetron prophylactically.

The PK study in 51 pediatric patients utilized a multi-center, two-arm, single dose design with doses of 0.1 milligrams per kilogram or 0.2 milligrams per kilogram IV. The results were that drug clearance was lower and half-life was prolonged in patients 1 to 4 months-old compared to those greater than 4 months to less than 2 years-old.

The population PK analysis combined data from the PK study and the CINV study, that I will describe in upcoming

slides. The population PK results were that 0.15 milligrams per kilogram per dose IV every four hours for three doses in cancer patients aged 6 months to 4 years-old resulted in systemic exposure levels similar to those achieved in older pediatric cancer patients at similar doses.

The PONV study in 670 pediatric patients was a multi-center double-blind placebo-controlled, randomized study of a single dose of 0.1 milligrams per kilogram ondansetron IV administered within five minutes following anesthesia induction.

The primary endpoint was the proportion of patients experiencing at least one episode of emesis during the 24 hour assessment phase. There were five secondary endpoints that included time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of patients receiving rescue medications and proportion of patients with emetic episodes

after the receipt of rescue medications.

For the PONV efficacy results, fewer patients experienced at least one emetic episode in the drug group at 11 percent or 38 out of 335 compared to the placebo group at 28 percent or 93 out of 335. In addition, the drug performed better than placebo in four of the five secondary endpoints, including time to first emetic episode, incidence of emetic episodes, proportions of patients receiving rescue medication and proportion of patients with emetic episodes after the receipt of rescue medications.

The CINV study in 76 pediatric patients was a multi-center, open-label study with three doses of 0.15 milligrams per kilogram ondansetron IV. This dose was based on the results of the PK evaluation, a review of the worldwide literature on the use of ondansetron in children, a survey of ondansetron use by pediatric oncologists and current prescribing information for the