DR. MASUCCI: Absolutely, and drug companies --

ACTING CHAIR WARD: Whoops. Oh, I'm sorry.

DR. MASUCCI: Go ahead.

ACTING CHAIR WARD: Does anyone disagree with this question?

PARTICIPANT: Does anyone think about the --

ACTING CHAIR WARD: Okay. Right. Okay.

DR. MASUCCI: But very tied to this is the second question.

ACTING CHAIR WARD: Yes.

DR. MASUCCI: For those drugs where it's not approved and we have limited data or data with some type of deficiencies, that needs to be made very clear in the label.

ACTING CHAIR WARD: Yes.

DR. MASUCCI: And if you --

ACTING CHAIR WARD: Right.

DR. MASUCCI: -- can certainly

recommend wording or context, that would be great.

ACTING CHAIR WARD: Yes. I think the wording has to be quite explicit to accurately reflect the data that you have, tested, not tested, shown to be ineffective versus inconclusive. Tom?

DR. NEWMAN: Yes, that's what I want to comment on. I would second that. I think efficacy not established is not the same as saying we recommend you don't use this because there are studies and we think it won't work or it would be harmful. And so if you say efficacy is not established and then down below, data inconclusive to warrant approval, those are too similar to each other.

So I would agree with others who have said that rather than efficacy not established, say not effective, do not use.

DR. MASUCCI: Right.

DR. NEWMAN: Yes, study shown to be not effective, do not use.

DR. MASUCCI: Right, the first question has to be --

DR. NEWMAN: As opposed to efficacy not established.

DR. MASUCCI: Right. The first question obviously is has it even been studied and then what did the studies find, and pertinent negatives are extremely important in this, in this context.

ACTING CHAIR WARD: Rich?

DR. GORMAN: Yes, sir. You know, the Agency has wrestled with exactly the same issue with pregnancy and came up with this lovely lettering system, which shorthanded this whole discussion we're about to have, never been tested in pregnancy, we don't know. It's terrible in pregnancy, don't ever use it.

And I know that's not the legal regulatory definitions of some of these letters. We don't have a lot of information, but it looks okay. We don't have a lot of

information, but it looks bad.

And I think a system like that where it could be graded as the initial sentence, and then you can go into as much detail as you want, would be very helpful where there would be four categories or five categories or one category.

Yes, you see, I make my life easy for everybody, don't I?

ACTING CHAIR WARD: I asked Dianne to just pull her hair out when we really got really far afield and I think we may be seeing that response. I'm not sure.

DR. MURPHY: You know, I understand why you're saying that, but actually there is an enormous effort to do just -- do away with that system because ob/gyn people have found it so unuseful and that they really want more information, and that what we have been trying to say and we have been actually telling the divisions, and Bob Temple has also made the statement, well,

maybe at least say, okay, it was studied in a trial of 29 kids, so you will know it wasn't like some adult studies, a 2,000 -- it mainly didn't work because you only did 29 kids.

We don't know, but that was the only information we had, that at this point we have been trying to push to get people to say what? A little sentence about what the trial was and then that it was not shown to be effective or not effective.

So that was sort of -- and not go into a categorization process, because people want to know what the basis of that categorization is and that is sort of where I think we're heading.

ACTING CHAIR WARD: We're going to let Rich respond in between apples here.

DR. GORMAN: I understand and I would also appreciate that extra information, but I will not discount the expertise that sits in this and the surrounding buildings to make a gradation that at least is an initial

stab for those of us who occasionally only read the Cliff Notes, okay, and don't get to the full novel.

DR. MURPHY: But there is never a novel for children.

ACTING CHAIR WARD: Right.

DR. MURPHY: There is only Cliff Notes for children.

ACTING CHAIR WARD: Short points.

DR. MURPHY: I shouldn't say that, the majority of the time. So I think that is why there has been a push to try to get whatever limited information we have without making it a novel that at least a study was done.

ACTING CHAIR WARD: Yes.

DR. MURPHY: That is number one. Everybody agrees that at least we got to put in there a study was done or not done, because as of last night I can tell you there are products in the PDR where we know we studied them and it's still saying safety and efficacy

not proven. So everyone agrees we got to get that fixed.

Secondly, we now are -- where do we put, you know, the information because the other thing that sort of happened that wasn't -- is that all the pediatric information now has been sort of in the Pediatric Use section. And some people are putting it there even if it's approved or unapproved and others are putting it in other places.

So that we're trying to bring some order out of this chaos and we have this wonderful group that happens to be looking at every one of the new labels that's done, so that we have this opportunity to do that.

So we're really -- they are coming to you to say do you like separating it out? There is a down side, I can tell you, of taking the approved pediatric information and putting it everywhere because, you know, some people just go to the Pediatric section now, which, you know -- when you only look at the

Cliff Notes.

But it also would make it a whole lot easier to have people understand that what is in the Pediatric Use section in the future would be those studies that were conducted, but did not result in approval.

ACTING CHAIR WARD: Okay. The down side of that, Dianne, is that that section will need to be able to be revised on a regular basis by the Agency as new data are published.

DR. MURPHY: If it's approved or not approved, but there is a supplement.

ACTING CHAIR WARD: This, the pediatric --

DR. MURPHY: There is a supplement.

ACTING CHAIR WARD: No, the Pediatric Use section.

DR. MURPHY: Right.

ACTING CHAIR WARD: Let's say it's the trial of 20 children and it was effective

in one or something like that. Next year there is another study of another. What are you going to do with that, so the subsequent study, the subsequent study that yet is still not approved and labeled for children?

DR. MURPHY: A sponsor would submit the studies trying to get an indication and, therefore, those studies would be looked at for whether they made that indication or not. If they made it, it would go in under making the indication. If it didn't, it would go into the Pediatric Use section.

ACTING CHAIR WARD: Okay. Then I'm confused. If there are data, published data that are not part of a sponsor's trial, can it show up in the label?

DR. MURPHY: It has to be submitted as a supplement.

DR. MATHIS: I think one of the big places where we're going to get these studies that don't demonstrate efficacy are from pediatric clinical trials as a result of

the Best Pharmaceuticals for Children Act. We have for a long time now really struggled with what to do with data from the studies that basically the taxpayer has paid for by blocking generics.

How do we get that information out to the public? And, of course, we have a couple of ways. We post the summaries on the web, but it has also been just recently, I think, that the entire Agency has accepted the fact that this information needs to get into labeling because pediatricians need to know that the drug has been studied and found to not be effective or inconclusive or that it works.

So we really have been using the Pediatric Use section of labeling for this additional information that we're getting from BPCA. I don't know that it would be possible for us to constantly scan the published literature and keep changing labeling.

ACTING CHAIR WARD: Next year

we'll start seeing controlled pediatric trials coming from Europe. So are you going to be putting those in or only those that the sponsor brings to you the data?

DR. MURPHY: Now, remember Labeling 101, that the label is owned by the sponsor and so the studies that -- they are the company that decides whether they want to get a new indication or not. And if they don't want a new indication and they don't submit it, then we would have to decide that we think there is a public health need because of some important information.

The division can go and ask the sponsor to submit it. They can do that. You know, there have been situations where something has come out in the literature. We don't just do labeling based on literature. We do labeling --

ACTING CHAIR WARD: That is not entirely true. If there is a toxicity issue, it will often land in the label.

DR. MURPHY: That's too broad of a statement.

ACTING CHAIR WARD: Yes.

DR. MURPHY: If there is a safety issue, I was getting ready to say, generally, for efficacy, you know, you want the raw data. You want to be able to look at it. If something comes up in the literature that there is a safety issue, people want that information, the division will request it, they will bring it in, they will look at it and they could put it in the label. But it would be a labeling supplement when they did that.

DR. JOHANN-LIANG: I have one thing. There is a mechanism. It's the citizen's petition mechanism where if you think there is a safety issue with a drug, anyone, you know, in the public domain could bring a citizen's petition into the FDA and the Review Division will look at that petition. They will still have to speak with

the sponsor to update the labeling though.

But there is a mechanism by which if you have, you know, an aggregate of trials, you know, in the published literature and you want to bring that in, so there is a mechanism.

DR. MASUCCI: Both the old labeling regulations and even now, even more explicitly in the Physician Labeling Rule say very clearly that the sponsor has to keep the labeling updated. And if new information becomes available, they need to incorporate it in their labeling or else their labeling is misleading. So they have some responsibility on that level to do that.

One quick comment about what Dianne said about keeping all the -- not keeping all the information in Pediatric Use for an approved indication, it does spread it throughout the label. However, what you would do in that Pediatric Use section is say, you know, two clinical trials were conducted,

demonstrated safety and effectiveness in kids over 12, See, Clinical Studies, See, Pharmacokinetics.

So the cross-referencing would be there to guide the reader so they wouldn't have to totally flip through the label by themselves. If they went to Pediatric Use first, they would be able to find everything they needed.

ACTING CHAIR WARD: Yes, Betsy?

DR. GAROFALO: Sure. I thought I would just make a couple of points. I think this is great. I like this proposal for the labeling and I think being more explicit with the pediatric information is better, because sometimes we don't have the luxury of doing as many trials, you know, in adults. It might take multiple depression trials to see an effect and we wouldn't necessarily have that luxury.

So to say it absolutely doesn't work may not be a fair assessment. So I think

more of the details as opposed to trying to draw some conclusion. And in terms of, you know, studies that are happening around the world and getting into our labeling here, I think most, you know, sponsors are very interested in getting the information out as well and are holding things back.

But it's really not any different between adult trials from pediatric trials. Some trials just don't ever make it into the labeling for one reason or other.

ACTING CHAIR WARD: All right. Given the --

DR. MURPHY: Question?

ACTING CHAIR WARD: Oops, sorry.

MS. DOKKEN: I just had a quick question, because you were talking about sort of guiding the reader, so they knew they would go to the Pediatric section and then they would know whether they were supposed to go every other place. Have you talked about whether there could be anything very quick and

easy that could be up-front in the Highlights, so you would know right away whether it was a yes or a no drug?

DR. MASUCCI: Now, that's a very good question. And Highlights is very -- is going to be very much on a case-by-case basis with each drug. One component that can go in Highlights, well, a couple of them where this information could find its way in is depending on the wording of the indication. If the indication is very explicit about the patient population that should be used, then that can be in there.

And again, the Physician Labeling Rule is even more explicit that the Indication section must include any important limitations to the indication. If we know it shouldn't be used in kids under 5, because of HP axis suppression, that should be an indication and that would find its way into Highlights.

Another section that can be incorporated into Highlights if there is

relevant information is a use in specific population subheading and the example that I gave you in your slides has that. Not every drug will have to say whether or not studies have been done in kids, yes or no. It is going to be a case-by-case review decision based on a couple of things on the relevance and the importance of the information.

Also, given the space limitations of Highlights, we are limited to half a page. So that's a constraint that we have never had to deal with before in labeling. And so those decisions are going to have to be made about priorities of information as well.

DR. MURPHY: Shall we go on to the last question? Are we through with this one?

ACTING CHAIR WARD: Does anybody disagree with this, given the comments from Dianne about the ownership of the label?

PARTICIPANT: Disagree with what?

ACTING CHAIR WARD: Pardon?

DR. MURPHY: I guess we just need

some summary, because there were some different, you know, discussion here. Does everybody agree that the language explained the lack of evidence for approval in the Pediatric Use section would be useful? Is that unanimous?

ACTING CHAIR WARD: I don't see a dissenting head nod.

DR. MURPHY: Okay.

ACTING CHAIR WARD: Okay.

DR. MURPHY: Okay.

DR. NEWMAN: Excuse me. But clarifying that, that the wording efficacy not established, not be used when the recommendation is not to use it, you know.

ACTING CHAIR WARD: Yes. I think from all of the discussion, I think, we have been pretty clear that we want explicit language about when it should and should not be used.

DR. MURPHY: Well, I think that's a good point to make though.

ACTING CHAIR WARD: Okay.

DR. MURPHY: That it needs to be better than the standard language.

ACTING CHAIR WARD: Yes, not established.

DR. MURPHY: And reflect the conversation of having more data than less within the restraints of what you all can do.

ACTING CHAIR WARD: Yes.

DR. MASUCCI: And we talked about this a little bit earlier about having a minimum age in indications. What I have seen within CDER is review divisions that have a lot of pediatric drugs, be it derm products or pulmonary with the asthma and the allergy products. A lot of them that have a lot of pediatricians on their staff, most of their labels have this, but other review divisions that don't, they don't.

ACTING CHAIR WARD: Yes, yes.

DR. MASUCCI: And I sense from our -- when we started with this topic that most

of you thought that was going to be very valuable information for the user.

ACTING CHAIR WARD: Does anyone disagree with this recommendation? Okay. We're moving on.

DR. NEWMAN: Thank you.

ACTING CHAIR WARD: Thank you.

DR. MASUCCI: Thank you all for listening.

ACTING CHAIR WARD: I think this will be more user-friendly and hopefully serve patients better.

DR. MASUCCI: Thank you.

ACTING CHAIR WARD: Tom is not finished yet. Hang on.

DR. NEWMAN: I just think this is wonderful and for all the reasons you mentioned, all labels don't work very well and this will be a huge improvement. But I'm just sort of dismayed that even in the year 2013, it is still going to be some like this and some like the old one. And the whole idea of

being okay, No. 1 means this, No. 2 means this. Can't we accelerate this process somehow?

DR. MASUCCI: In terms of getting labels changed from the old format to the new?

DR. NEWMAN: Yeah.

DR. MASUCCI: Well, we are seeing some of that. I mean, some -- there are already a handful of labels approved in the new format. Some companies are really eager to do this. They think it's better for them. They think for whatever reason, be it a marketing advantage, who knows what their motivations are, but I think we're going to see more rather than less.

DR. NEWMAN: Is this something FDA can regulate or make happen sooner?

DR. MASUCCI: Our regulations are very explicit about by when certain dates you must and beyond that is purely voluntary, but we are encouraging. In what form that encouragement is going to take, you know, arm

twisting, threats, I don't know. But I think, you know, for certainly older drugs, off-patent, no new studies, nothing else coming out, we're going to see old labels for a bit.

ACTING CHAIR WARD: Could I ask about why you made a cutoff of 2001 to have to do it?

DR. MASUCCI: I have no idea. I was not involved in that decision. Those people, I don't think are in the room.

DR. MURPHY: I don't know. I can just -- I just want to tell you guys that I won't tell you how many years it took to get this label. This is so exciting that we have it and it's going to happen in our lifetime. I know I'm strange.

ACTING CHAIR WARD: I though you were going to say you were in high school when it started.

DR. MASUCCI: Thanks again.

ACTING CHAIR WARD: All right. Alan is going to come back and we will return

to the abbreviated presentations of fully reviewed drugs, I should say. We will start with ritonavir.

DR. SHAPIRO: This is more of a standard presentation for this one, but that's okay. So I would like to continue on with the infectious disease theme and talk about the one year post-exclusivity adverse event review for ritonavir.

Ritonavir also known as Norvir is an HIV protease inhibitor. Its sponsor is Abbott Laboratories. Now, this is the prior to exclusivity the treatment, its indication was treatment of HIV-infection in combination with other antiretroviral agents greater in patients 2 years and older. It gained market approval in March of 1996 and pediatric exclusivity was granted in June of 2005.

One thing I want to emphasize which is very important about ritonavir, it's not being used the way it was studied. Right now, we're using ritonavir more as a metabolic

enhancer. I'm going to describe that here.

For all protease inhibitors, resistance has been reported when using monotherapy and can even develop when you are using combination therapy, in which drug levels are subtherapeutic. This could be due to inadequate dosing, poor drug absorption, rapid drug clearance and inadequate adherence.

As I started to mention, ritonavir is mainly now used to increase the serum concentration and decrease the dosage frequency of other protease inhibitors. "Boosted" therapeutic regimens usually consist of two protease inhibitors, usually a low dose of ritonavir plus saquinavir or lopinavir/ritonavir, which is also known as Kaletra, and combined with one or two Nucleoside Reverse Transcriptase Inhibitors. With the exception of lopinavir/ritonavir, there is limited data on the safety and dosing of combination protease inhibitor regimens in children.

Now, getting on to this. As I mentioned, that these studies, pediatric exclusivity studies are describing ways of using ritonavir that we're not currently using, but that still, at the time, was what people were interested in. So of the trials, there was initially a Phase 1/Phase 2 dose finding open-label study of two different doses of ritonavir used alone and in combination with lamivudine and zidovudine in HIV-infected infants and children.

This looked at safety, tolerance, pharmacokinetics and activity of ritonavir. And there was also a Phase 1/Phase 2 open-label management study in HIV patients 6 months to 21 years of age with rapidly progressive/advancing disease who is failing current therapy.

Now, the results of these trials was that there was no statistic difference between -- noted in the small randomized study between the dose of 350 milligrams per meter

squared and the 450 milligrams per meter squared twice daily doses during the first 104 weeks of follow-up with respect to HIV-1 RNA, CD4 cell count and CD4 percentage.

Overall, the toxicity profile of ritonavir seen during the clinical trials appeared similar to that observed in adults. Ritonavir was part of a combination antiretroviral therapy, therefore, it was difficult to determine the exact contribution of ritonavir to any clinical or laboratory toxicities and many of the approved antiretroviral drugs have overlapping toxicities.

Now, labeling changes that resulted from exclusivity studies for ritonavir. For the indication, extended the age range down from 2 years down to 1 month. Safety, the adverse event profile in the pediatric population was similar to that of adults and also PK and dosing information was added for pediatric patients less than 2 years

of age.

Now, to talk about the Adverse Event Reports since marketing approval. For all ages, there were 6,511 Adverse Event Reports of which 6,026 were serious and there were 703 deaths. In the pediatric age range, there were 417 reports, 380 were serious and there were 39 deaths.

Now, going on to the 13 months post-exclusivity period for ritonavir. For all ages, there were 984 reports of which 953 were serious and there were 183 deaths. Now, in the pediatric age range, there were 68 reports of which 63 were serious and there were 5 deaths. Although, I should emphasize that this represents three unduplicated pediatric deaths.

Now, in discussing adverse event types of ritonavir exposure, there are two types of exposure I need to emphasize. No. 1, you have the direct exposure, which are patients that receive treatment of HIV-

infection. This is usually in patients after birth who are using combination with other antiretroviral agents for HIV treatment. So it is difficult to assign causality to the reported adverse events.

And then there is indirect. This occurs in utero and that's for ritonavir being used during pregnancy by HIV positive mothers for maternal health and prevention of perinatal HIV. The caveats here are exposed infants may or may not be HIV-infected. There is possible association of combination antiretroviral therapy and premature delivery. And newborns receive antiretroviral therapy postpartum, which may complicate the interpretation of adverse events associated with the in utero exposure.

Now, in the adverse events from direct exposure to the one year post-exclusivity period, as you can see, the adverse events listed here include three deaths, seven hepatic events, five drug

interactions with fluticasone propionate causing Cushing Syndrome, two pancreatitis, two of gastrointestinal symptoms, three of drug being ineffective, three skin reactions, eight miscellaneous, which includes the ones listed below and the unlabeled ones which are underlying include: alopecia, nystagmus, strabismus and spontaneous abortion.

Now, I would like to go over the three pediatric deaths from direct exposure during the one year post-exclusivity period. The first one was a 16 year-old HIV-infected female on lopinavir/ritonavir, stavudine and lamivudine who died of cryptococcal meningitis.

There was also a 21 month-old HIV-infected patient on lopinavir/ritonavir, lamivudine, stavudine who died of cardio-respiratory complications secondary to disseminated cytomegalovirus infection.

There was also a 2 year-old male who died due to hemorrhagic pneumonia,

ruptured porencephalic cyst, medication error, bronchospasm and deterioration of renal function while enrolled in a clinical trial of atazanavir, stavudine, lamivudine and ritonavir.

Now, in utero exposure, as we talked about, most commonly reported adverse events were the fetal or intrauterine growth retardation. There were three reports. Three reports of neutropenia, two of anemia, two of hypertriglyceridemia and there was blood lactate or lactic acid increased. I should mention that all three of those patients were exposed to Nucleoside Reverse Transcriptase Inhibitors, both in utero and postpartum, which have been known to be associated with lactic acidosis. And one of CPK increased.

As mentioned before, the underlying ones, which are the intrauterine growth retardation and lactic acidosis is those that are not labeled in ritonavir.

Now, in utero adverse events, also

there were congenital anomalies, which were seven, which are listed below. One thing I should emphasize about the congenital anomalies, the interpretation of these in ritonavir exposed patients who are exposed are complicated by the health of the mother and the use of multiple antiretrovirals during pregnancy.

Lastly, I would like to mention in the in utero exposed there was one intrauterine death at 34 weeks gestation in a 35 year-old female on saquinavir, ritonavir, zidovidine and lamivudine who had severe endometriosis. The fetus was delivered following demise and nuchal cord was noted, but there was no apparent birth defects.

Now, going on to ritonavir drug use. Pediatric patients account for, approximately, .8 percent of Norvir prescriptions. The number of patients receiving Norvir over the pre- to post-exclusivity years increased 20 percent for

adults, but decreased 31 percent for pediatric patients age 0 to 16 years.

So in the post-exclusivity year, an estimated 765 patients and over, that's pediatric patients, 94,000 adult patients received Norvir prescriptions. The projected number of unique pediatric patients who received the dispensed prescription for Kaletra decreased by 8 percent from 2,600 in the pre-exclusivity year to 2,383 in the post-exclusivity year.

Now, to summarize for ritonavir, there are no concerning safety signals. HIV is a serious frequently fatal disease and antiretroviral therapy has many known serious adverse events. Causality interpretation also is confounded by concomitant medications.

This completes the one year post-exclusivity Adverse Event Reporting as mandated by BPCA. The FDA recommends routine monitoring of ritonavir for adverse events in all populations. Does the Advisory Committee

concur? And I would like to thank the following individuals who helped in the preparation of my presentation.

ACTING CHAIR WARD: Thanks, Alan. Committee Members, does anyone disagree with this recommendation? Okay.

DR. MURPHY: Let me throw in an extra question in here.

ACTING CHAIR WARD: Sure.

DR. MURPHY: One of the reasons we present some of these products not abbreviated to you is because they are, as I mentioned earlier, in conditions in which we know there are a lot of deaths. In a situation like this, where we do have a number of deaths and severe AEs, but we, you know, know that because of the disease there will be.

If we look at it and we don't see anything, would you be comfortable with us doing this as abbreviated, even though there are a large number of deaths?

ACTING CHAIR WARD: Anybody feel

that we need extra details if they have gone through this exhaustive review?

DR. MURPHY: Okay.

ACTING CHAIR WARD: Okay.

DR. MURPHY: You would still get the material.

ACTING CHAIR WARD: Yes.

DR. MURPHY: But again, we're trying to --

ACTING CHAIR WARD: Yes.

DR. MURPHY: We keep trying to slice and dice what it is you really want to hear about and now we have gotten down to deaths and serious AEs.

ACTING CHAIR WARD: Yes.

DR. MURPHY: There are certain conditions in which we anticipate there were, and if we don't see anything, we could present them to you as an abbreviated.

ACTING CHAIR WARD: I think that sounds very reasonable to me.

DR. MURPHY: Okay.

DR. SHAPIRO: I'm still here for the next one.

ACTING CHAIR WARD: Rapamune?

DR. SHAPIRO: Rapamune.

DR. PENA: Dr. Marc Cavaille Coll is also the representative from the division. He is a medical officer, team leader, Division of Special Pathogen and Transportation Products.

DR. SHAPIRO: Okay. Now, going on to a slightly different tact to an immune suppressant, sirolimus, and the one year post-exclusivity adverse event review. Sirolimus also known as Rapamune is an immune suppressant. The sponsor is Wyeth Pharmaceuticals. Its indication is a prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. It gained market approval in September of 1999 and exclusivity was granted in November of 2004.

Drug use trends in outpatient

setting for sirolimus. Pediatric patients accounted for 4.3 percent of the 165,000 Rapamune prescriptions dispensed in the U.S. from December 2004 to November 2005. The pediatric use of Rapamune increased from 4,900 prescriptions in the year prior to exclusivity to 7,100 prescriptions in the year following exclusivity.

Patients in the 12 to 16 year-old age group accounted for the majority of prescriptions dispensed to pediatrics in the post-exclusivity period with almost 60 percent of the annual Rapamune prescriptions dispensed to this older group of pediatric patients.

Now, going on to the exclusivity studies for sirolimus. The first study was a randomized study in high immunologic risk pediatric renal allograft recipients that compared the following regimens for safety and efficacy. The first was sirolimus plus calcineurin inhibitor, which could be either cyclosporine or tacrolimus and

corticosteroids.

The next was double therapy, which is a calcineurin inhibitor and corticosteroid, or triple therapy, which was calcineurin inhibitor plus azathioprine or mycophenolate mofetil and corticosteroids. The second study was a double-blind randomized trial of steroid withdrawal in sirolimus and cyclosporine-treated primary transplant recipients. I should emphasize that pharmacokinetics data was collected from both studies.

The results of these studies. Efficacy failure in the intention-to-treat population was numerically more frequent in pediatric patients randomly assigned to receive the combination of sirolimus and a calcineurin inhibitor than in the subjects allocated to a standard therapy. When comparing only patients 18 years or younger, efficacy failure rates were similar.

Adverse events such as abdominal pain, fever, abnormal renal function, urinary

tract infection were significantly more common in sirolimus-treated cohort than compared to standard therapy. The actually emphasized UTI rates were 15 percent in the sirolimus combination group versus 1 percent for the control group.

The pharmacokinetics of sirolimus and cyclosporine regimen. The younger children had overall lower sirolimus dose normalized to exposure, apparently due to higher clearance. There was a strong correlation at steady-state between whole blood sirolimus pharmacokinetics values were observed for all treatments and regimens. Sirolimus trough concentrations were adequate surrogates for sirolimus exposure.

Now, resultant labeling from these studies. We have information on the pharmacokinetics parameters. Safety and efficacy of sirolimus established in children 13 years or older judged to be, and I need to emphasize this, low to moderate immunologic

risk.

In pediatric renal transplant recipients considered to be high immunological risks, the use of sirolimus in combination with calcineurin inhibitors and corticosteroids were associated with, one, an increased risk of deterioration of renal function, two, lipid abnormalities and, three, urinary tract infections.

Therefore, to emphasize safety and efficacy have not been established in pediatric patients less than 13 years of age or in pediatric renal transplant recipients considered to be at high immunological risk.

The Adverse Event Reports since market approval for all ages, there were 3,712 reports of which 2,981 were serious and there were 375 deaths. In the pediatric age group, there were 88 reports of which 82 were serious and there were six deaths.

Now, the adverse events for the one year post-exclusivity period, for all

ages, there were 862 reports of which 845 were serious. There were 86 deaths. In the pediatric age range, there were 19 reports, all were serious and there were no deaths.

Now, going over the pediatric deaths in the post-marketing period. I would like to go over each of these six cases and also give an explanation of what we think was going on with each of these cases.

The first one was a 15 year-old recurrence of hepatoblastoma with fatal complications following liver transplant. I should emphasize that hepatoblastoma is a high-risk cancer in which the recurrence has been known in transplanted patients.

Also, there was a 10 year-old renal transplant patient with subsequent renal vein thrombosis and infarction of the donor kidney. This patient developed respiratory failure and cardiac arrest. One thing we need to distinguish with this case is whether it is the known transplant complication of renal

vein thrombosis versus being a sirolimus-related thrombosis.

Now, we have a 9 year-old with renal and cardiac transplant who developed severe thrombocytopenia and leukopenia three weeks after transplant who died three weeks later. One thing to note is sirolimus is associated with bone marrow suppression.

Now, there was also a 2.5 year-old patient with congenital genitourinary abnormalities who had a renal transplant who died of complications of aspergillus pneumonia and gastrointestinal bleeding. For this patient, we note the aspergillus pneumonitis and CMV colitis is known complications of immunosuppression.

Now, we have lastly a 6 year-old with short-bowel syndrome status post intestinal transplant who developed progressive encephalitis with elevated liver enzymes due to hepatitis A along with primary EBV and HHV-6 infection. Graft was removed

and immunosuppression was discontinued.

This patient subsequently developed erythroderma with severe edema and adenopathy following cytolytic hepatitis and eosinophilia. This patient died of multi-organ failure. Now, we know that exacerbations of EBV and HHV-6 infections are known complications of immunosuppression.

This is the last one. There is also a 12 year-old with end-stage renal disease, post-transplant diabetes mellitus, hypertension and renal hyperplasia status post renal transplant. Five months after being transplanted, the patient was hospitalized with viral lower respiratory infection with subglottic edema. This patient died following discharge. The death thought to be due to laryngeal inflammation and airway obstruction. This was likely an exacerbation of viral infection due to immune suppression.

Now, for the serious pediatric adverse events, there were 19 unduplicated

pediatric reports in patients on sirolimus during this one year post-exclusivity period. That consisted of eight patients with transplant complications and rejections, three gastrointestinal events, three drug interactions or drug level fluctuations of which two of them were due to possible interactions with azithromycin, which is not labeled.

There was also cardiac events, in which there were two, which were not labeled, infection and panniculitis and intracranial bleeding, both of which are not labeled for sirolimus.

Now, I would like to go over the pediatric adverse events for the two patients with interactions with azithromycin. The first patient was a 6 year-old renal transplant who was on sirolimus, tacrolimus, prednisone and co-trimoxazole. This patient was on azithromycin for pneumonia.

This patient had an overdose of

tacrolimus due to medication error and had increased tacrolimus and sirolimus levels and neurological side effects. Sirolimus levels continued to be elevated even though tacrolimus stopped. Only once azithromycin was stopped the sirolimus level decreased.

Now, the other patient was a 5 year-old renal transplant on sirolimus, tacrolimus, atorvastatin and ferrous sulfate who was on azithromycin for pneumonia. This patient developed increased sirolimus and tacrolimus levels with neurotoxicity despite having the sirolimus dose reduced.

From these two cases, we can say that they are confounded by tacrolimus overexposure, that the sirolimus label does not have any warnings about interactions with azrithromycin. But I should also emphasize that compared to other drugs, but not limited to ketoconazole and erythromycin, azithromycin is a weak CYP3A inhibitor. And we just indicated it as part of our concerns.

Now, for the cardiac adverse events, we had two, which I talked about, which are unlabeled. There is a 3 year-old renal transplant patient on tacrolimus and sirolimus with iron deficiency. This patient had fever and three months of history of cough.

The x-ray showed massive cardiomegaly and lung infiltrate. The echo showed moderate to large pericardial effusion. The viral work-up revealed only Adenovirus type 2 in the stool. This patient and a pericardiocentesis and the effusion stabilized and did not recur.

There was also a 2 year-old renal transplant patient with hypertension and a prior history of pericardial effusion on tacrolimus, prednisone and sirolimus who subsequently developed persistent pericardial effusion. The pericardial effusion increased in size despite decreasing sirolimus dose and was hospitalized twice for this condition.

During the second hospitalization it was noted to have an upper respiratory infection associated with fever, nausea and emesis. Following the second hospitalization, the pericardial effusion resolved on its own while on the reduced sirolimus dose. Currently, the Office of Safety and Epidemiology is evaluating the association of sirolimus use with pericardial effusion.

Now, to go on to the two other unlabeled adverse events, one being panniculitis. There was a 14 year-old renal transplant patient on azathioprine, prednisone, sirolimus and nitrofurantoin and enalapril who developed lower limb panniculitis two months after starting sirolimus and was hospitalized.

They continued the sirolimus for another seven months. This patient recovered following the discontinuation of sirolimus therapy. But I should emphasize that there are not enough information to make any

conclusions about this adverse event.

And for the intracranial bleed, there was a 2 year-old liver transplant patient with concurrent short-bowel syndrome on tacrolimus, prednisolone, sirolimus, loperamide and gentamicin who had treated with 2 milligrams of sirolimus for 28 days. The day after stopping sirolimus, developed an intracranial hemorrhage.

One and two weeks after the event, the brain scan still indicated new bleeding. The patient did recover from this event. The interval between transplant and intracranial hemorrhage was not known. I should emphasize that hemorrhage is a labeled adverse event and it's not clear if bleeding was related to the sirolimus since it occurred after it was discontinued.

Now, to summarize. The Office of Surveillance and Epidemiology and the Division of Special Pathogens and Transplant Products are evaluating the association of sirolimus

with pericardial effusion. The division is in discussion with the sponsor about potential labeling changes.

This completes the one year post-exclusivity Adverse Event Reporting as mandated by BPCA. FDA recommends routine monitoring of sirolimus for adverse events in all populations. Does the Advisory Committee concur?

I would also like to acknowledge the following individuals who helped me with my presentation.

ACTING CHAIR WARD: Any questions for Alan about the cases or the AEs?

DR. SHAPIRO: Okay.

ACTING CHAIR WARD: Geoff?

DR. ROSENTHAL: You know, this issue of pericardial effusion just has me baffled, but I have seen it clinically as well. Is this a complication that has been seen or an adverse event that has been reported in the adults on sirolimus?

DR. SHAPIRO: Yes, it has. And as we said, it's that we're currently following up with the Office of Surveillance and Epidemiology is looking into it and they are contemplating more of a thorough review at this time.

DR. COLL: Yes, in the published literature there have been a number of similar cases and we do know that this product probably has some effects on wound healing and intraproliferative effects. We are currently in discussion with the company on how better to describe this phenomenon in the label as it probably relates to several types of adverse events, including the pericardial thrombosis for which there is a black box warning.

ACTING CHAIR WARD: Have these been cultured for viruses and shown to be sterile effusions?

DR. COLL: In these cases here we do not have that information.

ACTING CHAIR WARD: All right.

Given the plans for more detailed monitoring of the pericardial effusion issue, does anyone disagree with routine monitoring at this point? Okay.

DR. MURPHY: And I guess the only other thing then is that we don't need to come back to the Committee with any more updates on the pericardial effusion or -- because right now the division is in the process of negotiating with the sponsor about a labeling change. So if they have a labeling change, do you want us to send it to you electronically? If they don't resolve that, do you want us to come back to you?

We didn't ask as a question, because we're -- those are what the points are about, bullet points. This is what's going on. Is there anything else you want us to do or just let you know if the label changes?

ACTING CHAIR WARD: Does that sound like adequate detail to something to receive the outcome of their deliberations

electronically?

DR. ROSENTHAL: Yes.

ACTING CHAIR WARD: Okay. So, Dianne, I think there is agreement that we would like to receive that information electronically and not have it reviewed and represented. Okay.

Did you get the short straw? All right. Alan will proceed, Invanz. I think we don't need a break right now, do we? Okay. All right.

DR. PENA: I will also mention that the representative from the division is Dr. Linda Forsythe. Dr. Forsythe is a medical officer in the Office of Anti-Microbial Products, Division of Anti-Infective and Ophthalmology Products.

DR. SHAPIRO: Okay. Being the ID person in this as part of Pediatrics Maternal Health Staff, I continue on with another infectious disease presentation.

ACTING CHAIR WARD: You can join

neonatology, I mean.

DR. SHAPIRO: So I would like to discuss the adverse event review for ertapenem. Ertapenem also known as Invanz is an anti-infective in the carbapenem class. Its sponsor is Merck. The indication is for treatment of complicated intra-abdominal infections, complicated skin and skin structure infections, community-acquired pneumonia, complicated urinary tract infections and acute pelvic infections. It gained market approval in November of 2001 and exclusivity was granted in February of 2005.

The exclusivity trials done for ertapenem include a single dose pharmacokinetics study in patients requiring antibiotic therapy, which also we had a single dose PK study of cerebral spinal fluid concentrations of ertapenem in patients with meningitis. There was also a double-blind multi-center comparative safety and efficacy study of ertapenem versus ceftriaxone for

community-acquired pneumonia, complicated UTI and skin and soft tissue infections.

There was also a double-blind perspective multi-center comparative study of ertapenem versus ticarcillin/clavulanate for the treatment of complicated intra-abdominal infections and acute pelvic infections.

The trial results include from the PK study, there was an appropriate dose of ertapenem determined to be 15 milligrams per kilo intravenously every 12 hours for patients 3 months to 12 years and 1 gram once daily for patients 13 to 17 years of age. One thing to really emphasize is that the CSF concentrations obtained were not adequate for the treatment of bacterial meningitis.

The safety profile of ertapenem in pediatric studies was similar to the comparators and similar to the profile described in adults. The most frequent drug-related side effect was diarrhea and infusion site pain.

Also, in the two comparative studies, the response rates of ertapenem versus the combined comparatives were similar. Now, to emphasize, safety and effectiveness of ertapenem also known as Invanz in pediatric patients 3 months to 17 years of age was supported by evidence from adequate and well-controlled studies in adults, pharmacokinetics data in pediatric patients and additional data from comparator controlled studies in pediatric patients 3 months to 17 years of age.

In the way of adverse events, there was no pediatric adverse events reported to AERS during the year following exclusivity, but there was two pediatric adverse events since market approval. And I will only discuss the serious one.

There was a 16 year-old male originally treated with ceftriaxone and clindamycin for periorbital cellulitis. This patient had a reaction to ceftriaxone and was

initially switched to metronidazole, vancomycin and levofloxacin and was subsequently placed on ertapenem.

This patient developed neurological changes, including agitation and combative behavior and diagnosed with a frontal brain abscess by CT scan. This improved following craniotomy and drainage of the abscess. Again, to emphasize, ertapenem is not recommended for the treatment of meningitis in pediatric population due to lack of sufficient CSF penetration.

Now, for the drug use of ertapenem. The pediatric use of ertapenem is relatively small, a total of 158 associated discharges from August 2004 to July 2005. During -- the pediatric use of ertapenem increased from 70 to 88 associated discharges from the six month period prior to receiving exclusivity as compared to the following six months.

Now, in summary, this summary of

ertapenem Adverse Events Reports is presented in abbreviated format, because, one, there are no concerning unlabeled safety signals, two, the pediatric use is limited with few Adverse Event Reports.

This completes the one year post-exclusivity Adverse Event Reporting as mandated by BPCA. The FDA recommends routine monitoring of ertapenem for adverse events in all populations. Does the Advisory Committee concur?

I would like to thank the following individuals for their help in this presentation.

ACTING CHAIR WARD: Robert?

DR. DAUM: Yes, so I'm not necessarily not concurring, but I do have a couple of questions.

DR. SHAPIRO: Yes.

DR. DAUM: What is the concentration of antibiotic in the CSF that is adequate to treat meningitis and how do you

know?

DR. SHAPIRO: That, you know, depends. As you know, it depends on the organism.

DR. DAUM: I don't know that I know anything. Invanz doesn't get into the CSF at all and treats candida meningitis in many instances just fine. And I think it underscores, I say it tongue and cheek, the fact that we don't really know what the right level is in CSF or rather if CSF is the appropriate place to look.

We measure it because it's there. Sort of like the Mt. Everest syndrome of meningitis, but I don't know how someone can conclude that the levels are inadequate to treat something unless you know something about the disease and how it performs.

DR. SHAPIRO: Yes. And, you know, I will just say one thing. It's that when we do make these decisions, and I can't really speak for the division, is that when looking

at an anti-microbial, you need to make some decisions of what you think is safe or not. And we only have this one case here which emphasized, you know, this patient had a brain abscess.

Whether it was related to poor penetration or not, it's not clear. But it's one of the concerns that was illustrated by the studies that were done, is that they were not finding a level which -- like I say, I cannot speak for the division, you know, that reached a level that they felt was sufficient.

DR. DAUM: Well, you preempted my second question and that is that a brain abscess is not meningitis. So I mean, there are some overlapping features of drug needing to cross blood-brain barrier and stuff like that, but it's not the same thing. I mean, is there any way to change that language so that it says the CSF penetration is not good or say what it is rather than the conclusion that it's inadequate to treat something? I mean,

you don't know that.

DR. SHAPIRO: Yes, like I said, as being not a member of the division, I can only reflect to you what basically was in the labeling and such. I would have to refer back to the division to answer that question.

DR. FORSYTHE: This is Linda Forsythe here. I mean, I think that's definitely a good point you have made. I know this was a clinical pharmacology issue and they felt very strongly about this wording at the time of approval. However, I think you bring a valid point. What are the levels and, you know, this could be something we can further address in our division.

DR. MURPHY: This is your area of expertise, so this is previous. You know, Bob has done a lot of work with meningitis. So I think the only way to answer that is that the biopharm people saw levels that were so low that they thought it would be inappropriate to recommend this for use of meningitis and that

the clinical studies, therefore, did not go forward. Is that correct?

DR. FORSYTHE: That's correct. That's correct.

DR. MURPHY: So that they did not, you know, request the study. So you are right in that they don't have the clinical trials to say it failed compared to some other product, but that's because they didn't think they should go forward because the levels were low.

DR. DAUM: I'm not even arguing with that decision. Mind you, I haven't seen the data you are talking about.

DR. MURPHY: Yes.

DR. DAUM: So I'm a bit in the dark here. But the point is that what you know is that levels on a limited number of patients in the CSF were very low. And why not just say that? I mean, why go further and talk about efficacy against a disease that we don't know how to measure or determine?

DR. FORSYTHE: Good point.

DR. MURPHY: They can go back and look at that language. But I think in general that if one sees very low levels, one would want to say we don't think this is a smart thing. I think that's sort of what they were doing, Bob, without having the clinical data supported.

DR. DAUM: I'm with you on that. I mean, vancomycin penetrates the CSF usually poorly and very variably between people.

DR. MURPHY: Yes.

DR. DAUM: But yet we recommend it for meningitis, don't we, because we don't really have anything better. And so I think that the correct way, if I were writing the vanco package insert here, I would say it penetrates the CSF poorly and variably. But yet, everybody recommends that it be a front line for meningitis of unknown etiology.

DR. MURPHY: And I would say that this division has people that know that and work with that all the time. So without again

having that individual data, all I can tell you is it must have been awfully dismal for them to come out and say we don't think we need a stronger statement in there. Because they are the people who know about vancomycin. I mean, they know all these models and that's the only justification I can come up with to say that they are familiar with it and this must have been very low.

ACTING CHAIR WARD: Can I just ask in adult studies are the same criteria applied and do they proceed similarly if CSF levels are quite low? Is that sort of routine?

DR. MURPHY: I don't know that it is routine. I wouldn't want to categorize it that way.

ACTING CHAIR WARD: Okay.

DR. MURPHY: Just because meningitis in the past has always been such a pediatric disease.

ACTING CHAIR WARD: Yes. Robert?

DR. DAUM: You know, I'm

uncomfortable with it.

ACTING CHAIR WARD: Okay.

DR. DAUM: I wouldn't vote for the language.

ACTING CHAIR WARD: Okay. Well, we're actually not voting on that language.

DR. DAUM: That's good. Then I have no issues.

ACTING CHAIR WARD: Right, right, right. You know, we just changed the state that's all. What I would suggest is that we ask you to take Dr. Daum's language back to the biopharm people as a concern by an authority in the field. And then -- but it would appear from the usage date we have and the toxicity data that there is not a striking signal of adverse events that need special attention.

So does anybody disagree with then routine monitoring at this point? Okay.

DR. MURPHY: Okay.

ACTING CHAIR WARD: Gemzar.

DR. SHAPIRO: Yes, I am moving on to an oncology product. Okay. Let's see, do we have a member of the division?

DR. PENA: Yes. The division representative is Dr. Martin Cohen. Dr. Cohen is a medical officer in the Division of Oncology Drug Products.

DR. SHAPIRO: Okay. Going on to gemcitabine, the post-exclusivity adverse event review. I also would like to acknowledge Solomon Iyasu who is familiar to the Committee who moved on to the Office of Safety -- sorry, Office of Surveillance and Epidemiology from pediatrics.

Gemcitabine also known as Gemzar is an antineoplastic agent. The sponsor is Eli Lilly. It is approved for breast cancer, non-small cell lung cancer and pancreatic cancer as first-line treatment in combination with other drugs. It gained market approval in May of 1996 and exclusivity was granted in January of 2005.

The use information for gemcitabine was difficult to obtain since the data resources available to us do not capture the use of gemcitabine in the outpatient clinic setting, which represents, approximately, 75 percent of its use.

We did use the Premier database which revealed pediatric use accounting for four discharges in which gemcitabine was billed between January of 2005 and June of 2005.

Now, the labeling that resulted from the exclusivity studies, the effectiveness of Gemzar in pediatric patients has not been demonstrated. There was a Phase 1 trial dose finding study in patients with refractory leukemia that found the max tolerated dose of 10 milligrams per meter squared per minute for 316 minutes, three times weekly, followed by one week rest period.

There was also a Phase 2 trial in

pediatric patients with relapse and acute lymphocytic leukemia and acute myelocytic leukemia and it was found that there was no meaningful clinical activity. The toxicities included bone marrow suppression, febrile neutropenia, elevation of serum transaminase, nausea and rash/desquamation.

For the adverse events, there was four non-fatal unduplicated adolescent pediatric Adverse Event Reports during the one year post-exclusivity period, which was confounded by concomitant medications and recent surgical procedure. There was also two fatal adolescent pediatric reports since approval of which one was during the post exclusivity period. Both patients died of disease progression, because they were refractory cases.

In summary, no new unexpected safety signals were identified in pediatric Adverse Events Reported through the AERS in the one year post-exclusivity period.

This completes the one year post-exclusivity Adverse Reporting as mandated by BPCA. FDA recommends routing monitoring of gemcitabine for adverse events in all populations. Does the Advisory Committee concur?

And I would like to thank the following individuals for helping my presentation.

ACTING CHAIR WARD: Thanks, Alan. Anybody disagree with moving this to routine monitoring? Okay. Welcome back, Lisa Mathis. And we will move to Ditropan, oxybutynin. Nope, I'm sorry. Whew, did I skip ahead. Okay. Amaryl, glimepiride.

DR. PENA: And the division representative at the table is Dr. Robert Misbin, a medical officer in the Division of Metabolism and Endocrinology Products.

DR. MATHIS: Dr. Ward, I do want you to know that --

ACTING CHAIR WARD: Yes, ma'am.

DR. MATHIS: -- we have already done the assignments for the next Advisory Committee and we took great mercy upon Alan. All right.

ACTING CHAIR WARD: Does that mean you got the short straw next time?

DR. MATHIS: No, I did not. I don't draw straws. All right. So I'm going to start with my discussion of Amaryl or glimepiride, which is an oral hypoglycemic agent by Sanofi Aventis US. It was originally approved in November of 1995 with pediatric exclusivity granted June 9, 2005.

There are some combination products that contain glimepiride. Those are Avandaryl and Duetact. Glimepiride is indicated for adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus. This drug is only approved for use in adults.

After the exclusivity studies, we did change labeling to reflect that data are

insufficient to recommend pediatric use. There was a single dose PK study as well as a 24 week clinical safety and efficacy trial that are included in labeling now. And also a statement that the adverse events were similar to those seen in adults.

In addition, there is a statement that hypoglycemia in this trial occurred 4 percent in patients compared to glimepiride, which was a comparator, where there was -- I'm sorry, metformin, which there was 1 percent of hypoglycemia.

All right. Drug use. The total dispensed prescriptions for glimepiride and related anti-hyperglycemic agents increased overall. Amaryl is the fourth most commonly dispensed product and pediatric use represents less than 1 percent. In addition, the use of Amaryl in the pediatric population has decreased since this drug was granted exclusivity.

Pediatric adverse events represent

less than 1 percent of the total of adverse events. Since approval, there have been only 8 out of 1,494. There were no pediatric deaths and there have been two confounded, non-fatal serious adverse events identified in pediatric patients during the post-exclusivity period.

One was in a 17 year-old with Trisomy 21 on amitriptyline who experienced behavioral abnormalities after two doses of glimepiride and one was in an infant with congenital anomalies, VSD, microcephaly, dysmorphic facies, after in utero exposure to a mother with a history of multiple miscarriages and two other children with congenital anomalies and consanguinity. I'm sorry. Okay.

In summary, as a result of the exclusivity studies, labeling indicates that there are insufficient data to recommend pediatric use. There are no new pediatric adverse events identified one year post-

exclusivity period.

This completes the one year post-exclusivity adverse event reporting as mandated by BPCA, and the FDA recommends that this product return to routine monitoring. Does the Advisory Committee concur? I better put up my thank you slide, too.

ACTING CHAIR WARD: Thank you, Lisa. Anyone disagree with returning it to routine monitoring or any questions about this product for Dr. Mathis? Looks unanimous. So we'll move now to NovoLog, insulin aspart recombinant.

DR. MATHIS: Okay. NovoLog or insulin aspart recombinant is a human insulin analog from Novo Nordisk Incorporated with original marketing approval in June of 2000 and pediatric exclusivity in May of 2005. It is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia. This is a drug that is dosed individually immediately prior to a meal.

Drug use trends. Dispensed prescriptions for NovoLog have been increasing with pediatric patients accounting for, approximately, 13 percent of prescriptions and the majority of pediatric NovoLog prescriptions have been to patients 12 to 16 years of age.

After the exclusivity studies, labeling was changed and NovoLog is indicated for use in pediatric patients. And just to piggyback onto the talk earlier about labeling, the indication actually states no age restrictions. It just states that it's approved for the treatment of diabetes.

PK and clinical studies are described and those studies went down to patients down to the age of 2. And, also, glycemic control and adverse events, particularly hypoglycemia, where comparable to those of regular insulin. That is included in labeling.

As far as adverse events since

marketing, for all ages there have been 1,338 with 616 serious and 36 deaths. For pediatrics, 154 with 72 serious and five deaths. Of those five deaths, there were four that were unduplicated. Two were infants. One was a 4 month-old female with truncus arteriosus communis and another was a 4 day-old male with hypoxic ischemic encephalopathy and seizures.

Also, there was a 14 year-old male with type I diabetes and a remote history of asthma who was found dead in bed. He had been treated for four to five months with insulin detemir and aspart, and post mortem the autopsy showed that his death was consistent with acute asthma attack, although he had not had an asthma attack in eight years.

There was also a 9 year-old male with type 2 diabetes on insulin glargine for six months and aspart for an unknown period. He died possible to alcohol overdose. It should be noted that while these four cases

were since approval, these are also four cases that show up here as three cases in the post-exclusivity period. The last patient, the alcohol overdose, was actually a patient that occurred after the data lock. We got this report in, so we just included it in here.

All right. Unlabeled serious non-fatal cases. In utero exposure accounted for four of these adverse events. So labeling has been updated after exclusivity studies. It is indicated for the treatment of type I diabetes in patients greater than 2 years of age, and the most frequent adverse event is hypoglycemia.

During the post-exclusivity period, although adverse events related to the in utero exposure were observed, there is no pattern and there are no new pediatric adverse events that have been identified.

This completes the one year post-exclusivity adverse event report as mandated by BPCA, and we recommend return to normal

monitoring. Does the Advisory Committee concur?

ACTING CHAIR WARD: Does anyone disagree with that?

DR. DURE: No, but how does a 9 year-old die of alcohol? I mean, was that a misprint on the age or what? Were there any more details?

DR. MATHIS: That was all the report said and I don't know if anybody else wants to comment, but it certainly is a reflection of some of the reports we get. There are questions that get raised. Was it a 19 year-old? Was it a 90 year-old? Was it alcohol poisoning? It's hard to tell, but that's what the report said.

ACTING CHAIR WARD: All right. Let's move on to meloxicam. Again, Dr. Mathis.

DR. MATHIS: All right. Meloxicam.

ACTING CHAIR WARD: Yes.

DR. MATHIS: You guys are getting sick of me now.

DR. PENA: I should mention that we have a division representative at the table.

DR. MATHIS: Thank you.

DR. PENA: Dr. Jeff Siegel, the medical officer at Division of Anesthesia, Analgesia and Rheumatology Products.

DR. MATHIS: All right. So meloxicam or Mobic is a nonsteroidal, anti-inflammatory by Boehringer Ingelheim. It had original market approval in April of 2000 and was granted pediatric exclusivity April 15, 2005.

It is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis for adults, and actually has a unique pediatric indication of pauciarticular and polyarticular course juvenile rheumatoid arthritis in children equal to or greater than 2 years of age.

The dosage for adults is 7.5 to 15 milligrams once daily, and that of children is 0.125 milligrams per kilo for a maximum of 7.5 milligrams once daily.

Drug use trends. Dispensed retail prescriptions for a group of nine NSAIDs, including meloxicam, have decreased by 21 percent. This may be secondary to some concerns about valdecoxib and rofecoxib which were withdrawn from the market in 2004 and 2005, respectively.

The dispensed prescriptions for meloxicam ranked fourth among the nine nonsteroidal anti-inflammatory drugs and pediatric use accounts for 0.3 percent of the prescriptions dispensed. It should be noted that most of the prescriptions are for an off-label indication of ankle sprains and juvenile osteochondrosis.

All right. Under the labeling changes that resulted from the exclusivity studies, we have a clinical pharmacology

section that says general trend towards lower exposure in younger patients 2 to 6 years of age compared to older patients, 7 to 16. The half life is slightly longer in younger patients and weight is not a predictor of clearance.

Also, there is information from two 12 week, double-blind, parallel-arm, active-controlled trials and an indication was granted that is unique to pediatric patients, JRA. Under the Pediatric Use Section of the Precautions section of labeling, it states that safety and effectiveness for pediatric JRA patients 2 to 17 years have been evaluated in three clinical trials. One was a PK study and two were safety and efficacy.

And the Adverse Events section reflects those adverse events seen in the clinical trials. The Dosage and Administration section of labeling includes dosage for pediatric patients.

And, in summary, there were no

pediatric adverse events identified during the one year exclusivity period. Since approval, there have been five pediatric adverse events, either labeled events or confounded, with the exception of one case of Bell's palsy in an athlete who received the drug for contusions.

This completes the one year post-exclusivity adverse event reporting as mandated by BPCA. And the FDA recommends routine monitoring of meloxicam for adverse events in all populations. Does the Advisory Committee concur?

ACTING CHAIR WARD: Does anyone disagree with that recommendation at this point? We're moving. Okay. I don't see any need for a break personally. I think we can move right on through. Okay.

DR. MATHIS: I will go quickly.

ACTING CHAIR WARD: Okay.

DR. PENA: I'll mention that --

DR. MATHIS: And that's no pun when you see what I'm going to talk about.

DR. PENA: The division representative is Dr. Mark Hirsch. Dr. Hirsch is the medical team leader in urology and Acting Deputy Director of the Division of Reproductive and Neurologic Products.

DR. MATHIS: All right. So I'm going to start with Ditropan or oxybutynin, which is an anticholinergic, antispasmodic by Johnson and Johnson originally approved in 1975. It was granted pediatric exclusivity February 8, 2002.

It is indicated in adults for symptoms of bladder irritability associated with voiding impatience with uninhibited neurogenic bladder, urgency, frequency, urinary leakage, urge incontinence and dysuria.

In children, it is indicated in patients greater than 5, greater than or equal to 5 years of age, for the regular release and in the XL or extended release, it's in greater than or equal to 6 years for detrusor muscle

over-activity in association with neurologic conditions such as Spina bifida.

The pediatric labeling. The labeling was changed as a result of pediatric studies. There is additional information on dose and PK parameters and also the Precautions section of the labeling is updated. Ditropan XL states that safety and effectiveness have been established down to 6 years of age.

As far as the pediatric adverse events go, when we initially came to the Advisory Committee in 2003 for the one year post-exclusivity update, there were only five unduplicated reports for one year and, at that time, it was determined that there weren't enough reports to really say anything, so we were told to come back and we have. And we have learned about the same thing, and that is that now we have 13 serious events, so we have only had 10 additional unduplicated reports in the pediatric population.

13 of the reports were considered serious. The most common were for an unlabeled indication, nocturnal enuresis. There were seven that were confounded by other drugs or underlying conditions or did not contain enough information to make a causality assessment. And the six remaining cases included one of extrapyramidal reaction in a 10 year-old boy. And then five remaining serious cases that were labeled events that may be due to the anticholinergic effects of oxybutynin, particularly anticholinergic CNS excitation.

When the Office of Surveillance and Epidemiology looked for these adverse events, they used some preferred terms indicative of CNS excitation and I have just listed them here, so you can see all of the terms that are covered by this umbrella CNS excitation title, and we think that these adverse events may or may not indicate increased sensitivity to anticholinergic

effects of this drug in the pediatric population.

We do know that some anticholinergics may cross the blood-brain barrier in pediatric patients more easily, but we also know that cholinesterase levels in pediatric patients are about the same as they are for adult patients. So we don't see a lot of increased anticholinergic activity otherwise.

The other thing is is that there may be differences in reporting rates for pediatric patients with CNS issues versus adult patients. All of the patients had other underlying neurologic conditions and were on other psychoactive drugs.

So, in summary, we saw no new safety signal. There were few reports, single cases. They were very confounded or had insufficient information and the FDA recommends routine monitoring of oxybutynin for adverse events in all populations. Does

the Advisory Committee concur?

ACTING CHAIR WARD: So we have an additional three years of data that doesn't point us in any particular -- to any particular area of concerns. Anybody disagree with discontinuing now at this point with routine monitoring? Okay. All right. Lipitor.

DR. MATHIS: It's not me.

ACTING CHAIR WARD: Okay. It will be presented by Jean Temeck, a medical officer.

DR. PENA: Dr. Temeck is in the Pediatric and Maternal Health Staff where she now functions as an acting team leader. She is board-certified in pediatrics and pediatric endocrinology. The division representative is Eileen Craig. Dr. Craig is a medical officer in the Division of Metabolism and Endocrinology Products.

DR. TEMECK: Thank you for giving me the opportunity to present to you today. I

really got the easy part, just presenting two updates to you and everyone else was doing all the hard work. And I want to thank my director, Dr. Lisa Mathis, for taking on all of Dr. Hari Sachs' drugs to present to you today.

Okay. Let's get Lipitor, this again is an update. We first presented to you back in June of 2003 the pediatric adverse events that occurred during the one year following granting of exclusivity to atorvastatin. So this is going to represent pediatric adverse events that has occurred in the subsequent three and a half year period.

Atorvastatin or Lipitor is a lipid-lowering agent. The sponsor is Pfizer. Original market approval was granted in 1996. Exclusivity was granted on February 22, 2002. The mechanism of action is inhibition of HMG-CoA reductase.

Atorvastatin is approved as an adjunct to diet in pediatric patients aged 10

to 17 years of age with heterozygous familial hypercholesterolemia and also for the treatment of homozygous familial hypercholesterolemia.

Since we presented to you in June 2003, labeling changes affecting pediatric patients entail implementation of a patient package insert. As you can see on this slide, pediatric use of atorvastatin is small, constituting less than 0.1 percent of the total number of prescriptions dispensed in retail pharmacies.

Just to refresh your memory, there were no pediatric adverse events during the one year following granting of exclusivity to this product. In the subsequent three and half year period, there have been 12 pediatric adverse events that have been reported. These 12 adverse events represent 0.15 of the total reports for all ages.

These reports were all serious and included one death. As you will see, that was

a stillbirth at 32 weeks gestational age. There were nine post-natal reports in children ages 2 to 16 years, which included three accidental ingestions exposures, ingestions and six other reports. The remaining three reports were in utero exposures.

Of the six reports that occurred in patients aged 4 to 16 years, three were labeled and included anemia, pancreatitis and elevated CPK with muscle stiffness. There were three unlabeled adverse events and they were bone marrow suppression, bronchospasm and hemoptysis.

The only information provided for the case of bone marrow suppression was that this was a patient who was 14 years-old and was taking 20 milligrams of Lipitor for the treatment of homozygous familial hypercholesterolemia.

The case of bronchospasm is a foreign report in a 4 year-old male who was taking atorvastatin and other medications for

myocardial ischemia. The bronchospasm recurred upon rechallenge times three, but details of the rechallenge were not provided. The event resolved, but the intervention taken was not reported, so this case was confounded by insufficient information and use of concomitant medications.

The final report, which is unlabeled, is that of hemoptysis, also a foreign report, occurred in a 16 year-old male who had been taking Lipitor and nicotinic acid to treat familial hypercholesterolemia. Bronchoscopy revealed diffuse pulmonary alveolar hemorrhage.

At the time of this report, this patient was also diagnosed with cardiac failure. Both medications were subsequently discontinued and we have no further information regarding this unlabeled adverse event.

So, in summary, regarding these post-natal adverse events that were unlabeled,

they were all either confounded by underlying illness, use of concomitant medications and/or insufficient information.

Now, we'll look at the three in utero exposures. These were all single cases and there was no pattern. They included one case of congenital blindness, one case of congenital hepatomegaly, single functional kidney and stillbirth at 33 weeks of gestational age with a maternal history of diabetes mellitus and use of multiple medications. The third case was one of congenital myopathy.

In summary, the pediatric unlabeled post-natal adverse events do not reveal a safety signal. There were few reports, single cases, that were confounded or there was insufficient information to assess them.

Regarding the in utero exposures, atorvastatin is Pregnancy Category X. FDA recommends routine monitoring of atorvastatin

for adverse events in all populations. Does the Advisory Committee concur?

ACTING CHAIR WARD: Thank you, Jean. Anybody disagree with continuing simply routine monitoring for atorvastatin? Okay. Statin on.

DR. TEMECK: Okay. Let's see here. Okay. Great. I will do a similar presentation now for simvastatin. Again, this is an update since we first presented to you in June of 2003, the pediatric adverse events that occurred following granting of exclusivity to simvastatin.

Simvastatin or Zocor is also a lipid-lowering agent. The sponsor is Merck. It was originally approved in 1991. Exclusivity was granted on February 22, 2002. The mechanism of action is inhibition of HMG-CoA reductase.

Simvastatin is indicated as an adjunct to diet in pediatric patients aged 10 to 17 years of age with heterozygous familial

hypercholesterolemia. It is also indicated for the treatment of patients with homozygous familial hypercholesterolemia.

Pediatric use of this product is small with pediatric prescriptions constituting less than 0.1 percent of the total number of prescriptions dispensed in retail pharmacies.

As reported to you previously, during the one year following granting of exclusivity, there were four confounded reports of serious pediatric adverse events, which included one death in a premature infant on day three. The infant had been exposed in utero to simvastatin.

During the subsequent, approximately, three and a half year period, six adverse events were reported in pediatric patients. These six adverse events constituted 0.13 percent of the total reports for all ages. They were all serious and included one death. There were, of course,

three post-natal reports and the other three reports were in utero exposures.

Regarding the post-natal adverse events, two of the reports are labeled and they constituted elevations in CPK, one which was also associated with muscle stiffness. The unlabeled adverse event was a case of thrombotic thrombocytopenic purpura in an 8 year-old female who also had systemic lupus erythematosus and Sjogren's Syndrome which, as you know, is associated with TTP, and this patient was also taking concomitant medications.

Now, this slide delineates the in utero exposures and, actually, we have three in utero exposures that were reported to AERS. However, one of these reports says that it was also reported in the literature and when we looked at the literature reference, it actually appeared to be an additional case, so there probably are four in utero exposures and I will briefly go through these here.

There were a spontaneous miscarriage. There was a skin outgrowth of the fifth finger of the left hand with an anomaly of the fingernail whose mother also took salbutamol during the seventh month of pregnancy. There was a case of lower limb deformity, which actually constituted a missing bone, tarsus bone, and also a shortened tibia and fibula on the right side as compared to the left.

There was maternal exposure to narcotics, as you can see here on this slide during the first trimester, and there was also one case of VACTERL association and use of concomitant medications.

To note that these drugs, all of these HMG-CoA reductase inhibitors, are Pregnancy Category X, the labeling does contain a statement that there are rare reports of congenital anomalies in infants whose mothers have taken these drugs during pregnancy.

In summary, we have one pediatric unlabeled post-natal adverse event that was confounded by underlying illness and concomitant medications. As I said, regarding the in utero exposures, these drugs are Pregnancy Category X. We recommend routine monitoring of simvastatin for adverse events in all populations. Does the Advisory Committee concur?

ACTING CHAIR WARD: Anybody disagree with moving this to routine monitoring? Okay. I will just observe the limb shortening and then the VACTERL or VATER, whichever form you care for, you know, looked like an interesting issue.

DR. TEMECK: Yes. The VACTERL actually, there is -- well, it's a non-random association of malformations as we know with sporadic occurrence and, actually, there is one other case of VACTERL association. It was with lovastatin and the mother also took dextroamphetamine during the first trimester

of pregnancy, so both of those cases -- those are the only two cases that I'm aware of.

And, actually, it's interesting that you bring up the point, because also the label for this drug class mentions that skeletal malformations have been reported in rodents, so I want to put that out as well, whatever, you know, that means.

ACTING CHAIR WARD: So we don't prescribe it to our pregnant patients. Okay. So we'll go forward there with the routine monitoring.

DR. TEMECK: Right. Thank you.

DR. MURPHY: I now have -- thank you very much, have a question for the Committee.

Having gone through now this process, this is like the third time we have done abbreviated and at the recommendation of the Committee, would the Committee -- there are a couple of options here. We can continue doing it the way we just have been doing it,

which we have tried to condense it down to not going through all the studies and, you know, just very quickly summarize.

We had hoped for three or four, sometimes it's five or six slides for the abbreviated, but the bottom line is we can continue doing that. We could get up and just basically say these are all of the drugs that we, you know, have reviewed and don't think they warrant even a standard presentation, there was very little data, and give you an opportunity from your reading to make comments and just say in general we think we would like to return to routine monitoring instead of going through each one of them. So that is --

ACTING CHAIR WARD: Yes.

DR. MURPHY: That's another option for the future that we are laying on the table for you for the abbreviated only.

ACTING CHAIR WARD: Committee Members and especially those of you who have been doing this for awhile, comments and

feedback to receiving the abbreviated discussions in a written or electronic format in advance? Larry?

DR. SASICH: The question that I would like to ask is if these are abbreviated and we don't get as much information as we do now, will these reports go through the Office of Drug Safety or the Office of Safety and Epidemiology?

DR. MURPHY: These reports are generated by them.

DR. SASICH: They are generated by them.

DR. MURPHY: Yes.

DR. JOHANN-LIANG: The one year post-marketing adverse event reports, not the ones with the exclusivity. That is done over at the --

DR. MURPHY: Right.

DR. SASICH: You --

DR. MURPHY: But the adverse event reporting is from the office.

DR. SASICH: But you know where I'm going is over the issue of an independent office of drug safety within the Agency and just how independent the safety people are at this point in time. Maybe it's a conspiracy theory again but --

DR. JOHANN-LIANG: We can have coffee later.

DR. SASICH: -- it's a safe question.

DR. MURPHY: I think --

DR. SASICH: That is kind of my concern. I was very pleased with what was done today, but I don't know. I mean, things become abbreviated and I get worried.

DR. MURPHY: Well, we don't want to -- we're trying to not balance not using your time ineffectively when we don't think there is anything there, because there is very little use, there is very -- nothing there. Yet, we want to adhere to the intent of making everything public and transparent.

ACTING CHAIR WARD: Yes.

DR. MURPHY: But if we can just, if we can condense. We don't want to condense it to the point where it's not useful, but I get the feeling when we have these ones that are so -- we already designated they are abbreviated.

ACTING CHAIR WARD: Yes.

DR. MURPHY: That it might be better to do it a different way, but if you don't want to, we can do that.

ACTING CHAIR WARD: I would think that we need just about the full amount of information we received.

DR. MURPHY: Right.

ACTING CHAIR WARD: But if we have the slide set and we have the background information, if we can read, we can work our way through this. And if questions arise, I think it's our obligation then to identify those and bring them back for further discussion.

DR. MURPHY: Okay. We'll try that the next time.

ACTING CHAIR WARD: Okay.

DR. MURPHY: For the abbreviated where we will -- we always try to get you the slide set, but particularly for the abbreviated --

ACTING CHAIR WARD: Yes.

DR. MURPHY: -- we will make sure we get you the slide set. It means that -- so that you will know what our thinking is, and we will have a session where we'll put all of them up and we'll have an opportunity for comments, how is that, instead of walking through each one of the slides? Okay. We appreciate that.

ACTING CHAIR WARD: Yes, I think that will work. Okay. All right. Let me, while everybody is still pretty much awake, go through some notes that I have about what we were going to ask in return for follow-up. Zyvox. We were going to receive follow-up on

cardiac events, especially those with elevated QTcs.

Avandia. We were going -- there was a recommendation that include in the label studies that did not show effectiveness, so it had been studied and they failed to show effectiveness.

DR. MURPHY: Well, it's in the label. The recommendation was to put it in the patient part of the --

ACTING CHAIR WARD: Okay.

DR. MURPHY: Yes.

ACTING CHAIR WARD: Yes. The whole issue, as Larry has emphasized this time, about information to patients I think will be an ongoing dialogue.

Trileptal. We wanted to see the results of the 2,000 pediatric patients in this large study, especially with respect to neuropsychiatric events, and then with respect to Trileptal and angioedema, anaphylactoid reactions, that was I think going to be

followed up as well if there was a signal. If there was not a signal, not.

Is that what you have down, Dianne?

DR. MURPHY: I have down that for Trileptal that you definitely wanted the division to come back and present what they found from those 170 studies.

ACTING CHAIR WARD: Yes, right.

DR. MURPHY: Of particular interest to you all was the subset analysis of the 2,000 or more that there will be, because they don't have all the studies in now, but that for the angioedema and anaphylaxis that whatever changes they were going to put into the label, that they didn't have to come and go through all that with you.

ACTING CHAIR WARD: No.

DR. MURPHY: You have heard this before. You just want to have sent to you in writing --

ACTING CHAIR WARD: Right.

DR. MURPHY: -- what the change for that was.

ACTING CHAIR WARD: Yes.

DR. MURPHY: Okay. Great.

ACTING CHAIR WARD: That's as I recall it as well. For Tamiflu, we already have scheduled a one year follow-up that will represent a two year follow-up from the first time the issues were raised about again neuropsychiatric behavioral changes, and a recommendation for a U.S. pediatric randomized controlled trial.

For Celexa, I had down that we were recommending stating the number of negative trials and wanted then to also receive the results of this review of QTc changes for SSRIs as a class recognizing that that may take awhile to accomplish. Yes, Robert?

DR. DAUM: Can you clarify something that I probably just nodded off while you -- wouldn't have happened. I don't

remember hearing a call for a U.S. controlled trial with Tamiflu.

PARTICIPANT: I don't know that it was U.S. either actually.

ACTING CHAIR WARD: It was from Tuli, Tuli Cnaan.

DR. DURE: It was an observational study.

PARTICIPANT: Observational.

DR. DURE: She talked about some observational data.

ACTING CHAIR WARD: Really? Okay.

DR. DAUM: I don't know if we called for it.

ACTING CHAIR WARD: That is why we're going through this.

DR. DAUM: Yes, I don't know if we called for it.

ACTING CHAIR WARD: Okay.

DR. DAUM: I mean, she called for it.

ACTING CHAIR WARD: Okay.

DR. DAUM: But not controlled.

ACTING CHAIR WARD: Yes.

DR. DAUM: I didn't hear any controlled stuff like --

ACTING CHAIR WARD: Okay.

DR. DAUM: -- there would be a placebo group or something.

ACTING CHAIR WARD: Yes.

DR. DAUM: I didn't hear that.

ACTING CHAIR WARD: Yes.

DR. MURPHY: Well, and we are trying to differentiate out. It was just an individual Member's recommendation from the entire Committee, such as the suggestion for putting the negative studies in the Celexa. That was an individual, I believe, for Celexa, but you do want to receive the QT information.

PARTICIPANT: Yes.

DR. MURPHY: The whole Committee said that. So for the Tamiflu, it was an individual recommendation that was made by?

ACTING CHAIR WARD: I think it was

an individual's recommendation. I don't think it received much discussion.

DR. MURPHY: Okay.

ACTING CHAIR WARD: Tom?

DR. NEWMAN: Yes, my thought about it would be I think she said that in order to disentangle whether it's due to flu or the drug, that it would be good to have a control group. I heard her say something like that.

ACTING CHAIR WARD: Yes.

DR. NEWMAN: So I understood a randomized trial. My concern would be if these psychiatric effects are very rare, I mean, there are millions of prescriptions in Japan --

ACTING CHAIR WARD: Yes.

DR. NEWMAN: -- and, you know, for something that is one in 10,000 or something, a big randomized trial to look at that adverse effect is not going to be feasible.

ACTING CHAIR WARD: Right.

DR. MURPHY: So?

ACTING CHAIR WARD: Any other, yes, Keith?

DR. KOCIS: I just thought earlier on we had that whole discussion about what trials should or could be done and what the FDA had authority on and I thought we came to the agreement you can't even encourage that other studies be done.

ACTING CHAIR WARD: Yes.

DR. KOCIS: Or did I misinterpret his comments from --

DR. MURPHY: We're just trying to capture what you guys recommended.

ACTING CHAIR WARD: Yes.

DR. MURPHY: We let you know that we can't make them go do it. Okay? We can't make them go do it. We can say, you know, this is what was thought to be useful.

ACTING CHAIR WARD: Yes, yes.

DR. MURPHY: And they can do what they wish to do. So we're just trying to make sure we understood what was being discussed.

Because were running so far behind, we began to get a little abbreviated there.

ACTING CHAIR WARD: True. Yes?

DR. KOCIS: I mean, we could recommend for every drug that a randomized, double-blinded, you know, I mean --

ACTING CHAIR WARD: Right.

DR. KOCIS: So I wonder where.

ACTING CHAIR WARD: Yes. Well, I think the issue is particularly difficult for Tamiflu because of this entanglement of disease and drug and the reactions that have been observed, but I don't know what the consensus of the Committee is about that.

Let me just ask. Do people want to recommend to the Agency to recommend a controlled trial? Do we want to try to get more data about influenza from Japan? What are some other options? Yes, Rich?

DR. GORMAN: I am unaware, being a simple country pediatrician, but is there any large group of people who are routinely

prophylaxed that we could follow observationally, people with immunosuppressive diseases perhaps? Do they get routinely prophylaxed, because I don't know that group.

And the second thing with the -- this is one of those cases where there will be a collision of the therapeutic imperative and new technology with the proliferation in this particular year of inexpensive, rapid influenza tests that are CLIA-waived, notice how there was all those qualifiers, that can differentiate A from B. Increasing Tamiflu use will probably be likely.

DR. MURPHY: Okay. What we will do, we'll go back and look at the transcript and see what we thought was being recommended by our statistician and then if there are no other recommendations from the Committee as a whole, we'll just note what the recommendations were from the statistician. Is that acceptable to the Committee then?

ACTING CHAIR WARD: I think that's

reasonable.

DR. MURPHY: Okay.

ACTING CHAIR WARD: Because it was not discussed and I think it was not a consensus.

DR. MURPHY: Yes, it wasn't.

ACTING CHAIR WARD: Okay.

DR. MURPHY: And I want to make it clear. We didn't think the whole Committee came to a consensus.

ACTING CHAIR WARD: Yes.

DR. MURPHY: We're just trying to pick up little pieces of individual discussions --

ACTING CHAIR WARD: Okay.

DR. MURPHY: -- that come out, too.

ACTING CHAIR WARD: All right. Tom, yes?

DR. NEWMAN: Just while we're on Tamiflu, a question I had that I didn't get a chance to answer. My impression was that the

use in Japan was almost all therapeutic rather than prophylactic, but I never got any actual numbers on that.

You know, if a whole many of the millions of prescriptions in Japan were prophylactic and this doesn't happen then, it would point a little bit more towards the flu rather than the drug as the cause. It doesn't mean that there isn't some interaction between flu and drug.

DR. DAUM: It was on the slides.

DR. MURPHY: And, Tom, all I can--

DR. DAUM: I think almost none of it was prophylactic.

DR. MURPHY: My recall to last year was that the way I think the division went through it is that what happens is that because of the health care system and the fact of the use of the rapid diagnostics, that they just go into wherever, local ER doctor, they get a rapid test and they get the medication. So it tends to be more treatment was what my

understanding of it last year was.

DR. JOHANN-LIANG: But your point is well-taken. I don't think we have specifically asked Japan to give us a breakdown of their prophylactic use versus their treatment use, especially in the most recent years as the prophylaxis indication was approved earlier in Japan than in the U.S. actually.

So that is a good -- that is something we can't -- we will have to go through Roche to ask for that, you know, query that for the Japanese data, but we can do that. But also the point is that for the numerator, for the adverse events that we have seen, almost all of it is, you know, the patient got a rapid diagnostic test done, took Tamiflu, one dose, two doses later. So that is a good point.

ACTING CHAIR WARD: But since we have closer working relationships with their regulatory agency over the last 5, 10 years,

it would seem to me an opportunity for us to be out ahead of the curve of use by asking them if they would provide us data and if they would increase their monitoring. It would be, I think, to their advantage as well as ours.

DR. MURPHY: We can certainly ask for that analysis of what breakout for prophylaxis use, prophylactic use.

ACTING CHAIR WARD: Folks, I think we are through. Dr. Murphy, any --

DR. MURPHY: I have two other things. One was under Tamiflu, there was some discussion about, you know, the labeling and the fact -- though I did find out that labeling is in print, but we will be coming back next year and we can, you know, re-discuss this, but there was a suggestion that the wording should have been different and that it should have been stop your medication while you're waiting to call your doctor versus call your doctor. So we did hear that.

And on Rapamune I have that you

want us to send the labeling changes just to you electronically, that we don't have to represent it to you, but you would like to know if there are any labeling changes particularly related to the pericarditis.

DR. DAUM: Regarding the comment that was just made about we don't know whether it was prophylactic or not, what was presented this morning were that there were 129 reports. 26 were excluded because they weren't certain about them, so there were 103. 95 were from Japan, five from the U.S. and three were other. Of those 103, three were prophylactic and 100 were therapeutic. I mean, that's --

DR. NEWMAN: And I'm asking, I mean, does that reflect the proportion of usage in Japan?

DR. DAUM: Ah, that's why we're here this morning.

DR. NEWMAN: Yes.

DR. DAUM: Yes. I think that is a great question.

DR. MURPHY: Yes, yes, we think we all agree. That's a good question. We'll try to go back and see if they can give us that information before next year.

ACTING CHAIR WARD: Thank you all very much, a lot of work, a lot of thoughts. We appreciate it.

DR. MURPHY: I also want to thank you all very much for sitting through 16 products and for your discussion and comments. Hopefully, we won't have so many next time.

(Whereupon, the meeting was concluded at 4:14 p.m.)