U.S. FOOD AND DRUG ADMINISTRATION

+ + + + +

PEDIATRIC ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

TUESDAY,
NOVEMBER 18, 2008

+ + + + +

The meeting was held in the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland, at 8:00 a.m., Marsha D. Rappley, M.D., Chairperson, presiding.

COMMITTEE MEMBERS PRESENT:
MARSHA D. RAPPLEY, M.D., Chairperson
CARL D'ANGIO, M.D., Member
AMY J. CELENTO, Patient-Family Representative
AVITAL CNAAN, Ph.D., M.S., Member
LEON DURE, M.D., Member
HENRY FARRAR, M.D., Pediatric Health Organization Representative
BRAHM GOLDSTEIN, M.D., MCR, FAAP, FCCM, Industry Representative
MARK HUDAK, M.D., Temporary Voting Member Consultant
MELISSA MARIA HUDSON, M.D., Member
KEITH KOCIS, M.D., M.S., Member
KATHLEEN J. MOTIL, M.D., Ph.D., Member
DANIEL NOTTERMAN, M.D., Member
ALEXANDER T. RAKOWSKY, M.D., Member
GEOFFREY L. ROSENTHAL, M.D., Ph.D., Member
ELAINE VINING, Consumer Representative

FDA PARTICIPANTS PRESENT:

CARLOS PEÑA, Ph.D., M.S., Executive Secretary
OZLEM BELEN M.D., Division of Special Pathogens and Transplant Drug Products
VICKY BORDERS-HEMPHILL, Pharm.D., Office of Surveillance and Epidemiology
BILL BOYD, M.D., Division of Anti-Infective and Ophthalmology Products
PATRICIA BROWN, M.D., Medical Officer, Division of Dermatology and Dental Products, Office of New Drugs, CDER
FELICIA COLLINS, M.D., M.P.H., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
JUDITH COPE, MD, MPH, Medical Officer, Office of Pediatric Therapeutics
SUSAN CUMMINS, M.D., M.P.H., Senior Science Advisor, Pediatric and Maternal Health Staff
CAROLE DAVIS, D.O., M.P.H., Division of Neurology Products
IDA-LINA DIAK, Pharm.D., Office of Surveillance and Epidemiology
ELIZABETH L. DURMOWICZ, M.D., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
NORMAN HERSHKOWITZ, M.D., Team Leader, Division of Neurology Products
DEVANAND JILLAPALLI, M.D., Acting Team Leader, Division of Neurology Products
THOMAS LAUGHREN, M.D., Director, Division of Psychiatry Products
NAOMI LOWY, M.D., Medical Officer, Division of Metabolism and Endocrinology Products
LISA MATHIS, MD, Pediatric & Maternal Health Staff, Office of New Drugs, CDER
MITCHELL MATHIS, M.D., Deputy Director, Division of Psychiatry Products
ANN McMAHON, M.D., Office of Surveillance and Epidemiology
DIANNE MURPHY, M.D., Director, Office of Pediatric Therapeutics, OC

FDA PARTICIPANTS PRESENT (Continued):

ROBERT "SKIP" NELSON, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, OC
PHILIP SHERIDAN, M.D., Medical Officer, Division of Neurology Products
AMY TAYLOR, M.D., M.H.S., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER

ALSO PRESENT:

RAMA BHAT, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
TODD GRUBER, M.D., M.P.H., Head, U.S. Medical Function, Novartis

TABLE OF CONTENTS

P R O C E E D I N G S

(8:03 a.m.)

CHAIRPERSON RAPPLEY: Well, good morning, and thank you to everybody for coming out today.

I think we'll start with introductions. Amy, would you mind if we start on your end?

MS. CELENTO: Amy Celento, patient representative.

DR. CNAAN: Avital Cnaan, statistician, Children's National Medical Center.

DR. D'ANGIO: Carl D'Angio, neonatologist, University of Rochester.

DR. DURE: Leon Dure, child neurologist, University of Alabama at Birmingham.

DR. FARRAR: Hank Farrar. I'm the pediatric health organization representative, and I'm a clinical pharmacologist at Arkansas Children's Hospital.

DR. GOLDSTEIN: Brahm Goldstein. I'm the pharmaceutical industry representative. I'm a pediatric critical care physician, and I work at Nova Nordisk in Princeton, New Jersey.

DR. HUDSON: Melissa Hudson, pediatric oncologist, St. Jude Children's Research Hospital in Memphis.

DR. KOCIS: Good morning. Keith Kocis from the University of North Carolina, and I'm a pediatric cardiologist and intensivist.

DR. MOTIL: Kathleen Motil from Baylor College of Medicine. I'm a pediatric gastroenterologist.

DR. NOTTERMAN: Daniel Notterman from the Department of Molecular Biology at Princeton University, and I'm also a pediatric intensivist.

CHAIRPERSON RAPPLEY: Marsha Rappley. I'm Chair of the Committee, and my area is developmental and behavioral

pediatrics.

DR. PENA: Carlos Pena, senior science policy analyst, FDA, and Exec. Sec. to the Pediatric Advisory Committee.

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

DR. RAKOWSKY: Good morning. My name is Alex Rakowsky. I'm the IRB Chair at Nationwide Children's Hospital, Columbus Ohio.

MS. VINING: Good morning. I'm Elaine Vining. I'm the consumer representative of the Committee.

DR. HUDAK: Hi. I'm Mark Hudak. I'm a neonatologist from the University of Florida, Jacksonville.

DR. LISA MATHIS: I'm Lisa Mathis. I'm Associate Director in the Office of New Drugs within CDER at the FDA for the Pediatric and Maternal Health staff, and I'm a general pediatrician.

DR. MURPHY: I'm Dianne Murphy. I'm the Director of the Office of Pediatric Therapeutics in the Office of the Commissioner, and I'm a pediatric infectious disease specialist or I was about ten years ago before I came to the agency.

DR. BOYD: Hi. I'm Bill Boyd. I'm an ophthalmologist in the FDA's Division of Anti-Infective and Ophthalmology Products.

DR. COPE: I'm Judy Cope. I'm a pediatrician, adolescent medicine specialist, epidemiologist in the Office of Pediatric Therapeutics.

CHAIRPERSON RAPPLEY: Dr. Pena has some words for us.

DR. PENA: Good morning to members of the Pediatric Advisory Committee, public attendees, and FDA staff. Welcome to this meeting.

The following announcement addresses the issue of conflict of interest with regard to today's discussion, reports by

the agency as mandated in Section 17 of the Best Pharmaceuticals for Children Act on adverse event reports for Betoptic, Aldara, Lamictal, Levaquin, Sandostatin, Zyprexa, Risperdal, Lamisil, Timolol, and Ambien.

The Committee will be provided a written follow-up report on Zyvox as requested by the Committee at the November 16th, 2006, Pediatric Advisory Committee meeting.

The Committee will also be updated on other activities, including the June 9th and 10th, 2008, Pediatric Ethics Subcommittee meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the Committee participants, it has been determined that Committee participants do not have financial interests that present a potential for conflict of interest at this meeting. In general, the Committee participants are aware of the need to exclude themselves from involvement in discussion of

topics if their interests would be affected, and their exclusion will be noted for the record.

We would like to note that Ms. Amy Celento is participating at the pediatric health care representative. Ms. Elaine Vining is participating as the consumer representative, and Dr. Hudak is participating at a temporary voting member.

We would also like to note that Dr. Brahm Goldstein is participating as a non-voting industry representative acting on behalf of the regulated industry.

Dr. Henry Farrar is participating as the non-voting pediatric health organization representative, acting on behalf of the American Academy of Pediatrics.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

We have one open public comment period scheduled for approximately 1:30 p.m.

I would just remind all to turn on your microphones when you speak so that the transcriber can pick up all that you state and turn them off when you're not speaking.

I also request that all meeting attendees turn their cell phones and BlackBerries to silent mode.

Thank you.

CHAIRPERSON RAPPLEY: Dr. Murphy.

DR. MURPHY: First of all I wanted to again thank everybody -- I'm afraid our IT person is going to have to find my slides on here for me -- for being here this morning and for agreeing to the four set dates that we have for this coming year as far as time commitments on your agenda, in addition to the other meetings that we've also asked this very busy Advisory Committee to participate in.

One of the things we're going to do this morning is to look at the agenda from the

perspective of your new work load, and we're going to do this because we have good news and bad news. The good news is that children are after a decade now of legislation and new legislation that's reinforcing this approach finally getting studied or at least they're getting the products that are being used in the pediatric population, are finally getting studied, and we have a lot of activity going on in the way of pediatric trials.

That brings with it, of course, the responsibilities of making sure that these trials are well designed and implemented ethically, and you are involved in a number of those issues, have been in the past, will be in the future, and this Committee also being specifically mandated to look at the safety, post marketing safety of these products after they have been granted their exclusivity under BPCA and now under FDAAA, which gets to your workload issue, for all of the products that are studied under either BPCA or PREA, and the

products that will be labeled as the new legislation says, because pediatric studies are so limited in number that any study done under these initiatives will have its results commented on in the labeling so that the public will be aware and the practitioners and prescribers that at least some study has been conducted and what the results of that study are.

And I comment on that, again, because it is unlike the adult universe at FDA where if you have a negative study, the information doesn't normally go in the label, but for pediatrics, the outcome of a negative or inconclusive study will now be recorded in the label. And the labeling is what's going to trigger your safety review.

What the Food and Drug Administration's Amendments Act are so fondly called, FDAAA, has done for you, has expanded your responsibilities to include, as I said, pediatric safety reviews for products studied

and labeled under the Pediatric Research Equity Act, and what this slide should say, in addition to your already identified responsibilities to do such under the Best Pharmaceuticals for Children's Act.

The requiring labeling about pediatric studies performed under these, as I've said, will be specifically noted irrespective of the outcome or approval status, marketing status for that product, for those studies for that product.

This has more than doubled your workload, and just to hammer home this, from June of '03 to March of '08, there have been 79 products that have been reviewed at 13 sessions. You have basically reviewed two to 16 products per session, and the only reason we've limited the number of products to two sometimes is because you've had additional issues to deal with, be it an ethics issue or a science issue or a protocol design issue at a meeting, and so we've only had time for a

couple of products.

Otherwise, most of the time we're bringing between eight to 11 products to you at each session. We tried to bring you the infamous 16-wheeler or 16 products one time. There was just so much information because each product comes with basically five different documents -- you can do the math -- that you had to plow through that you asked us to please not do that again.

I told you yesterday that we weren't going to do it again, and then I turned around and said, well, we really are and it's actually going to be 19, but we're going to do it in a different way, and we'll get to that in a minute.

So in five years you had 79 products that you reviewed. We still have 11 products remaining that need to be reviewed from the BPCA. Since FDAAA has been enacted in September of 2007, we have 36 new labels. We have more than that since I prepared this

slide, but actually 36 new labels so that you have 47 products that will need to come for review before the end of 2009.

We're going to actually do some of those today, but the point being there were almost 80 in five years, and you're now going to have approximately 40 in one year. So it doesn't take very much to figure out you're going to be very busy, and that these product reviews will now include biologics and vaccines as far as the safety, and there are additional responsibilities for devices, which we reviewed in your training session yesterday.

We will before the end of 2009 be bringing some biological products to you in vaccines, and yesterday you received some additional information and training on how those safety reviews will be different or the same.

We've had this issue of trying to make this process more efficient and

fundamentally the previous Committees have said don't just give us the top 20 adverse events. Give us the serious and life threatening adverse events and the deaths. We want to see all of those reported to us.

And you have struggled with how to put all of this in context when you don't really have a good numerator or denominator, and we reviewed yesterday for you in your training session the agency's approaches to trying to provide that kind of information for you.

Some of that comes in the form of trying to put these adverse events in context, and so we provide you a very, very succinct and summary review of what the exclusivity studies were, focusing on the safety component. We will be doing that for the PREA studies also, pediatric studies under PREA, again, focusing on the safety issues that may have arisen during those control trials in addition to the adverse events.

We also and by law now look at -- we have always been mandated to look at all of the adverse events for adults and children, but now the law also says since marketing. So we try to put in context for you the adverse events that are pediatrics in the context of what's been happening with the product both for adults and since marketing. That is a big task, and we try to condense it down for you and pick out, again, those areas that we think need to be focused upon, and that's why you will see sometimes in these reviews the safety reviewer who will say we've been asked to focus on the following. It's because we get together with the divisions and the pediatric staff and the safety reviewers and talk about what are the issues that might be already existing with these products.

It doesn't mean that you can't bring up another topic, but that's just the consensus within the agency of where we think the issues might be.

The other thing that we've done in the past is we've tried to classify the reviews, the presentations -- let me correct that -- the presentations into three categories: either an abbreviated presentation, a standard presentation, or an expanded presentation.

The Committee made it very clear to us that they were all right with us having shorter presentations as long as they got all of the materials to review, and that's going to be relevant to the next process that we're trying to implement.

So what we had been doing is we've been giving you very brief presentation for the abbreviated products, not going through all of the exclusivity studies, not going through all the background with them, and all I can tell you is maybe it's just human nature. Maybe it's that we always find it interesting. Our brief presentations we're expanding. We found that we really weren't

getting a real reduction in time and effort, and we were spending time on products that didn't really have any signals and really didn't have any issues.

So what we are now proposing is that if we have identified a product as abbreviated, you will get the full package that you always have, but we are not going to do a presentation. These are products that we've identified as not having any signal at all, not even a question, not a lot of deaths. Sometimes there are hardly any use.

So what we will be doing is you'll see today for the ophthalmologic products that we are going to put up a slide and ask you if you have any questions that have resulted from your reading of the materials that we've sent you for those products which have been identified as abbreviated.

So because the law wants to make sure that we have public input into this, you will have an opportunity to ask questions, but

we aren't going to do a presentation.

The other thing that is happening is that follow-up reports that you have asked us for, if they do not have any signal or we have no, you know -- you asked us to monitor to see if there were any continuing deaths or serious adverse events and we really don't have anything that's remarkable that we can report back to you, we are going to do the same thing for those follow-ups.

Instead of standing up and going through the whole history of what has happened, we're going to provide you that information in the package, but we are not going to do a presentation. We will put up a slide and ask you if you have any questions, and there will be an opportunity for you to ask questions, and you will see that we've done that for Zyvox today.

The standard will be the same. Now, we say standard or expanded. Does that mean we identify the signal? The answer is

no. It means that it's a complicated review because either the underlying disease has a lot of deaths or a lot of complications, people are on a lot of concomitant meds, there are a lot of adverse events, there's a lot of use; it's just something we don't feel comfortable saying we don't think it needs a public presentation.

Often you'll see the majority of the products that we present to you, over 67 percent of them will have a recommendation just to return to routine monitoring, but we feel that because of the complexity of the disease and the adverse event reporting that we need to at least have a public discussion.

This is something for you to be thinking about because you're going to see we're going to ask you for feedback in the future. Is there anything that we should be doing with the standard reviews to somehow reduce that type of time utilization?

The expanded may be a new product

that's come or it may be one like we have today for octreotide where the Committee struggled with the issue of does this product have any relationship to these adverse events that we're seeing in the necrotizing enterocolitis, the hypoxia.

And they said okay. There was a good discussion. The Committee really could not come to any conclusions and said we have some recommendations about labeling at this point, but if we do that, we want to make sure that it's clear that we're not making any causality statement.

And you asked us to continue reviewing and bring it back to you. So in an effort to bring that discussion to some sort of conclusion, we've brought in a neonatologist who is involved with this product to discuss what's going on out there in neonatal medicine and the use of this product, and then we've given you the background information on the discussion

before, and we'll be asking you today for your recommendations.

So that is how we're approaching the future. The abbreviateds are being even more abbreviated. There will be no presentations. You will be receiving packages for reading only from the follow-ups. There will be opportunities for comment, but we are hoping to reduce the time that we are spending and, therefore, the number of days of meetings that we have to have you here because we know there are other ways that we'd like to use your time.

Now, as I said, we've already asked you to hold four dates for this year. We know you have other things to do besides safety review, and the approach that I've just described, however, helps us with some of the time management for scheduling how much time we need you here, but in truth, it does not decrease your work burden. You still have to read all of the background material, you know,

look at the five different documents that comes for every single one, and for some of them that are expanded, you'll be getting literature reviews. You may be getting extra safety reviews. You may be getting extra materials. So it really doesn't reduce your time.

And so we are going to be asking you after our June meeting, which you are going to receive approximately, we think at this time, around nine products with an abbreviated review, plus the others which will be somewhere between the standard and expanded, where we'll be asking you to be providing us feedback as additional ways to make this process more effective or efficient so that we don't undermine the intent of this, which is that there is a focused pediatric review.

Because you saw in your training yesterday that the adverse event reporting for the agency is going up overall, but not for

kids, and it's a very little, teeny part of the adverse event reporting, and if you don't go in and retrieve it and pull it out and look at it separately, you're not going to find signals for children.

So that's the intent of this process. We don't want to undermine that. We want it to be a robust process, but we have to face the reality that you guys can't have additional housing in Washington so that you can be here all the time to do the safety reviews.

So on to today. You're going to get the follow-up report only or you already got it for Zyvox. We'll have an abbreviated presentation for the two ophthalomogic products, Betopic and Timolol, and these, I'm not going to read the list of all the products for a standard review and one expanded update.

You're one of the busiest of FDA's Advisory Committees, and as you know, we appreciate your commitment and expertise, and

we figure that working together we will solve this problem. I know with all of the good minds around this table, we'll figure out a way to make this a robust process that focuses on the things that are really necessary to focus upon.

And, again, we look forward to your discussion today, and thank you very much for your time.

Now, Judith, do we have the first slide? Do you want to come up and put the slides up?

CHAIRPERSON RAPPLEY: While Dr. Cope is getting ready, I just want to make a comment that I will try to keep us on schedule and on time in respect of everybody's time today.

Thank you.

DR. COPE: Okay. In your package, you should have gotten a follow-up report on Zyvox or linezolid. So as Dr. Murphy said, we're starting the abbreviated review. This

was a follow-up from I believe it was November 2006.

There was a question of cardiotoxicity and overall there wasn't any safety signals or concerns. So we're asking you if you had any questions about the report. Yes.

DR. KOCIS: Of course I'm going to extend this from the beginning. So actually I agreed with the conclusions about the review for the peds review and the lack of cardiac toxicity, but then I get to the end and then I see that the FDA is requiring a clinical trial to look at prolonged QT. So there set me back a little bit in examining the cardiac cases that I reviewed and didn't feel there was a signal to now. Is there information that I need to know or will know or other information that could change what I'm going to say?

DR. COPE: Okay. We have somebody sitting here from the division. I think that my interpretation was that was all ages, but

I'm going to let Dr. Boyd. Would you like to come up?

DR. BOYD: Sure. I'm Bill Boyd. I'm an ophthalmologist, but I'm in the same division as the anti-infective folks. They're at a different advisory meeting. Let me try to answer that.

I spoke with the Deputy Division Director, and the reason that they requested that study is the explanation was at the time they did the original studies for the approval of the product, they didn't have the methodology in place to do this type of testing. They want to be complete. They're not convinced that because of the severity of illness in the population that they're studying that they're going to be able to determine if there's absolutely no safety signal. It's part of a mechanism they prefer to go ahead and just have the trial performed, but it is going to be all ages.

DR. KOCIS: And I just bring that

up because any time you're looking at sudden in children and prolonged QT being a rare event, it would be in the same light. So I'm glad they're going to look at that and particularly look at it in children.

DR. MURPHY: I thought you all might ask that because again, it is a confirmatory approach. It's trying to be as thorough and gather as much data as they can, but at this time we really couldn't see any signals.

Somebody was talking about all of the acronyms yesterday. When I was re-reviewing that last night, you know, all of those acronyms in the data mining are explained in the back. So I do hope you got to the back of that review.

Okay. Thank you.

So we, therefore, will return this product to the Committee if anything comes from that review when those studies come in, because I think that's what the recommendation

from the OSE said, and otherwise we will not be bringing it back to you.

Is that acceptable?

CHAIRPERSON RAPPLEY: Anybody opposed to that?

DR. GOLDSTEIN: I have a quick question and follow-up to Dr. Kocis. Given the rarity of these events, is that request feasible?

DR. MURPHY: The study you're talking about?

DR. GOLDSTEIN: Yes.

DR. MURPHY: Do you want to make any comments on that?

DR. BOYD: My understanding with our QT study group is that the request is it is possible it will achieve its objective. I know that the protocol has been submitted and is with that group now for review. I actually don't have more information than that, but my understanding is it has the potential to answer the question they're asking.

CHAIRPERSON RAPPLEY: Thank you.

Next.

DR. COPE: Okay. As Dr. Murphy talked about, this is another abbreviated slide we have in your package, are two ophthalmologic products, the betaxolol HC ophthalmologic suspension, or Betopic, and the timolol gel forming solution.

And with the reviews that you received and all of the work that the team has done, we see that FDA will continue its standard ongoing safety monitoring for these products. That would be the FDA plan, and so I ask you: does the Committee concur?

CHAIRPERSON RAPPLEY: Question?

DR. KOCIS: Again, I just have another process question on both of these drugs, and again, I agree with the safety of them, but I was confused. I remember talking about this the first time we looked at the drugs.

When we talk about safety and

efficacy, you use the phrase that efficacy has been extrapolated from the adult data for both of these drugs, and I'm left in looking at the adult data that's shown in the package insert where the drop in the IOP was much greater than the data that were presented for the drop in the intraocular pressure in children.

I'm not an ophthalmologist, and I don't know what to expect for things like that, and while clearly there's a statistical difference in intraocular pressure, in the pediatric trials that looked at this, it wasn't of the same degree as it was at least in the charts in my reading of the adult data.

And so I'm confused as to why we're splitting efficacy and safety in children or why we don't report the efficacy findings under the pediatric section along with the safety rather than deferring to the adult data to support efficacy.

CHAIRPERSON RAPPLEY: Dr. Boyd.

DR. BOYD: Let me make sure I

understand your question. You are asking about the difference in the IOP lowering effect in children versus adults, and it is difficult to measure IOP in children. It doesn't mean it can't be done and it doesn't mean it's not accurate. There's just a tremendous amount of information on adult IOP lowering versus pediatric patients.

We routinely, when we have studies, do not specifically request that children be excluded. So some of the newer trials have far more children than some of the older.

As far as why is there a difference in the IOP lowering amount, I don't have a good answer for you, other than I think it's a statistical effect. There's no reason for me to suspect that there's a mechanistic reason for the IOP lowering effect to be different.

DR. KOCIS: My only point is that when you look at the adult data, my read -- I'm not an ophthalmologist and I don't want to try to interpret these, and I believe efficacy

was proven both in adults and in children based on the approval process.

What I'm saying though, if you're extrapolating pediatric efficacy based on the adult data, my read on the significance on the drop in IOP and adult data is, you know, a lot different than what numbers we're seeing for the drop in IOP in children, and my only point would be I would say in the pediatric section specifically what the decrease in IOP was from these studies just because we have the data; you know what the numbers are. How you interpret it as an ophthalmologist, I'll leave that to you, but I don't want to mislead pediatric practitioners that you're going to see the same effects in the adult studies in the pediatric studies because at least my read of the data, that's not the case, and again, I think there's lots of reasons to think that increased intraocular pressure in children, neonates, et cetera, can be a very different disease than adults.

DR. MURPHY: Okay. So I just want to clarify because yesterday during training we talked about extrapolation. So you're not really asking about the extrapolation. You're accepting that the division said they can't extrapolate because the disease is similar and they often expect the same response.

Your question is why that response is different.

CHAIRPERSON RAPPLEY: No.

DR. MURPHY: No?

CHAIRPERSON RAPPLEY: I hear Dr. Kocis' question as we have pediatric data. So why don't we comment on that data in the label?

DR. MURPHY: Well, that's what I was getting ready to say. Why don't we say something about the difference? It's not whether you can extrapolate. It's that you did extrapolate, but you had data that showed that the response -- remember if you go through extrapolation, you meet those two

criteria of the disease and the response or you think it is and you do hypothesis testing and you see that it does, which is sort of the situation which you're describing now, and you have differences. So why not put that in the label?

But that's your question. It's not a safety question. It's a labeling question.

DR. KOCIS: It's specifically a labeling question, and the consistency of the safety and efficacy from the peds data being in the peds label rather than splitting it and saying, well, we're going to show efficacy from the adult studies, but then safety from the peds studies. It's incongruent in my thinking.

DR. LISA MATHIS: I think one thing to be really careful about is when the pediatric studies are intended to support extrapolation, they are not powered to demonstrate the same effect as you're seeing in adults. So it may be misleading to put the

information in there in a way that seeks to directly compare the efficacy.

So I hear what you're saying. Maybe next time we'll look at this and consider putting the data into the label, but we'll have to do it in a way that doesn't mislead clinicians and patients to believe that there perhaps is less efficacy in the pediatric population simply because the studies weren't powered to demonstrate that.

DR. KOCIS: I would just go back to we have pediatric data which is rare, and when we have it, we should include it and then clearly we can put all of the caveats that there's power to show this and there was a range of effect and, you know, put it into the clinical context, but we have the data, and it seems less than ideal to not include it in the label.

CHAIRPERSON RAPPLEY: Dr. Mathis, when would be the next time when you referred to next time?

DR. LISA MATHIS: Perhaps the next time a product comes in. I'm not sure if going back and changing this label that was actually done a year ago is going to provide any clinical benefit to patients. So I'm saying the next time that a product comes in or the next time perhaps that this product comes in with another application, that might be a time to address it.

But from a workload standpoint I'm not sure how much bang we'd get for our buck going back and changing this label. I don't think that that's the intent of this Committee either.

CHAIRPERSON RAPPLEY: Dr. Kocis, do you feel you've made your point?

DR. KOCIS: Yes, I've made my point.

CHAIRPERSON RAPPLEY: Thank you.

DR. KOCIS: You know, the pediatric labeling, I know that that's our focus to strengthen that part, and I think we can

strengthen it in these two drugs.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: I guess the message back to the division from the Committee, if I can summarize, is that in light of the intent to get information in the label, even when you are extrapolating, if there's a way when you see differences like that in that part where you're doing, again, I call it hypothesis testing that you can extrapolate and you have the data; if there's a way to put it in the label so that physicians understand because I think Lisa's point is really critical that it's not that it was inferior. It's just that it was limited data, and it had an effect, okay, and this is the range of the effects.

That would be the recommendation of the Committee for future approaches to the labeling of these products.

CHAIRPERSON RAPPLEY: Maybe any time we have pediatric data we would like to be able to refer to it with all of its

limitations clearly described.

DR. BOYD: For whatever reason when people study IOP lowering drugs, it's very common to see one or two millimeters of decrease even in people who receive the placebo all the time. So that's some of what you're seeing with the pediatric data. There just aren't as many patients, but I understand what you've brought up today, and I'll take that back to the division.

CHAIRPERSON RAPPLEY: So the question before us then for these two medications, that is, betaxolol and timolol, the statement is FDA will continue its standard ongoing safety monitoring for these products. Does the Committee concur?

Is anyone opposed?

So there is consensus on the Committee.

DR. COPE: Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Our next is Risperdal and Dr.

Collins.

DR. MURPHY: Just before we go forward, Lisa made a point which I think we brought it out yesterday, but let's put it in the public realm since we did mention it yesterday about the opportunity now. We have with FDAAA for reviewing labeling. Do you want to address that, Lisa?

DR. LISA MATHIS: We do have the Pediatric Review Committee now. So we do look at labeling prior to approval, and so there will be more opportunity to provide feedback to the divisions before approval occurs, and I think that we actually are trying to make sure that data does get into labeling if we have it.

So we'll address that in the future. I just want you to know that we have more opportunity to do that now.

DR. MURPHY: And, Marsha, because actually we failed, meaning FDA failed, to ask to do this one time and it resulted in the

Committee not being aware, the people at the table, I wanted to make sure that when we have the different people come up for the different products that we're introducing the speaker, but I'd also like to have the people at the table from the division who are here to please introduce themselves.

DR. LAUGHREN: I'm Tom Laughren. I'm the Director at the Psychiatry Products Division.

DR. MITCHELL MATHIS: And I'm Mitchell Mathis, the Deputy Director of that same division.

DR. MURPHY: Tom, would you just tell them your background?

DR. LAUGHREN: I'm a psychiatrist by training, and I've been with FDA roughly 25 years.

DR. MITCHELL MATHIS: I'm a psychiatrist and family practitioner by training, and I've been with FDA for about eight years.

DR. MURPHY: Felicia, would you introduce yourself, please?

DR. COLLINS: Sure. Good morning, everyone. My name is Dr. Felicia Collins. I am a general pediatrician within the Pediatric and Maternal Health staff with the clinical practice area exclusively in adolescent medicine.

And this morning I'm pleased to be able to present to you the one-year, post exclusivity adverse event review for risperidone.

Oral Risperdal, or risperidone, is an atypical antipsychotic for which Janssen is the drug sponsor. Original market approval occurred on December 29th, 1993, and pediatric exclusivity was granted on February 28th, 2007.

Prior to the pediatric exclusivity studies, oral Respirdal was indicated for the treatment of schizophrenia in adults, the short-term treatment of acute manic or mixed

episodes associated with Bipolar I Disorder in adults, and the treatment of irritability associated with autistic disorder in children and adolescents.

The next two slides provide information about the use of risperidone in out-patient settings. Seven, point, eight million oral risperidone prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. Ten percent of these prescriptions were for adolescents, 13 to 17 years old, and 15.5 percent were for children zero to 12 years old.

There was a two percent increase in prescriptions for all age groups between the 12-month pre and post exclusivity period and a ten percent increase for the pediatric population. Psychiatry was the top prescribing specialty during the post exclusivity period. All psychiatrists prescribed 53.4 percent of all oral

risperidone prescriptions. Child psychiatrists prescribed 11.4 percent of all prescriptions. Pediatricians prescribed 3.6 percent of all prescriptions and child neurologists prescribed one percent of all prescriptions.

The top diagnosis codes associated with oral risperidone use by children zero to 17 years old were infantile autism and attention deficit disorder.

On November 25th, 2002, the FDA issued a written request for studies of oral risperidone in the acute treatment of schizophrenia in pediatric patients 13 to 17 years old and in the acute treatment of mania and Bipolar I Disorder in pediatric patients ten to 17 years old.

The resulting pediatric exclusivity studies included five studies: one pharmacokinetic study, three efficacy and safety studies, and one safety study.

The results of the submitted

pediatric exclusivity studies indicated that risperidone is effective and reasonably safe for the studied indications in pediatric patients.

The following two slides list all of the labeling sections that were changed based on the results of the pediatric exclusivity studies. Changes were made to the indications and usage section, dosage and administration section, adverse reaction subsection on commonly observed adverse reactions in placebo controlled clinical trials on discontinuations due to adverse reactions and on changes in ECG to the use in the specific population section, pediatric use subsection, and to the clinical study section.

The next five slides will provide details of selected labeling changes. The indication and usage section was changed to extend the schizophrenia indication to adolescents 13 to 17 years old, and to extend the bipolar mania indication to children and

adolescents ten to 17 years old.

The dosage and administration section was changed to note that no additional benefit was seen above three milligrams per day in the schizophrenia studies or above 2.5 milligrams per day in the bipolar mania studies.

In addition, this section notes that for both indications higher doses were associated with more adverse events.

The adverse reaction section, discontinuations due to adverse reaction subsection was changed to note that for the schizophrenia studies approximately seven percent of patients discontinued in the risperidone group versus four percent in the placebo group.

Adverse reactions associated with study discontinuation in the risperidone group included somnolence, dizziness, anorexia, ataxia, hypotension, and palpitation. This subsection also was changed to note that for

the bipolar mania studies 12 percent of patients discontinued in the risperidone group versus seven percent in the placebo group. Adverse reactions associated with study discontinuation in the risperidone group included somnolence, nausea, abdominal pain, and vomiting.

The use and specific population section, pediatric use subsection was changed to note that for the schizophrenia studies 14 percent reported a weight increase and open label studies, and there was a mean weight increase of nine kilograms after eight months of treatment in 103 adolescents.

For the bipolar mania studies, it was noted that increased body weight was higher in the risperidone group than the placebo group, although not dose related.

This subsection also was changed to note that somnolence was the most commonly observed adverse event in pediatric schizophrenia and bipolar disorder trials. In

addition, the subsection notes that in controlled pediatric schizophrenia or bipolar disorder trials, hyperprolactinemia was seen in 82 to 87 percent of children and adolescents in the risperidone group versus three to seven percent in the placebo group.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports since marketing approval. For pediatric patients there were 1,535 adverse event reports which comprise 7.5 percent of the total reports.

Of these reports, there were 48 death reports with 33 being U.S. cases. Of the 48 crude count pediatric death reports identified since marketing approval, 17 of these were duplicates. Of the 31 unique pediatric cases, four involved an indeterminate cause of death, and the 27 remaining cases involved ten nervous system, nine cardiac system, and eight miscellaneous

cases.

After reviewing the 31 unique pediatric death cases, the safety reviewer did not identify any new safety concerns. There are multiple sections of the drug labeling that are relevant to the pediatric death cases. The warnings and precautions section of the drug labeling include subsections on seizures, neuroleptic malignant syndrome, hyperglycemia, and diabetes mellitus with worsening glucose control, orthostatic hypertension, and suicide.

The adverse reaction section of the drug labeling includes arrhythmia, hypotension, pulmonary embolism, and cardiopulmonary arrest.

The next several slides provide more details for the 27 death cases, and you will note that unlabeled events have been underlined. Of the ten nervous system cases, five cases involve adolescents who died after a seizure or related complication while on

risperidone.

Two cases involve patients with a history of epilepsy and one additional case involved concomitant paroxetine use, which has a labeled seizure association.

The sixth case involved a seven year old who experienced encephalitis, hypotension, arrythmia, and cerebral edema, and died two days after risperidone therapy.

There were three cases involving children who died of neuroleptic malignant syndrome, or NMS-like symptoms while on risperidone. Of note, one case involved concomitant medications with a labeled NMS association.

And the last nervous system case involved a nine year old who died due to a cavernous angioma 12 days after initiating risperidone therapy.

For the cardiac cases, two cases involved children who died from cardiac arrest while on risperidone without concomitant

medications, but these case reports lack significant details.

And two additional cases involve children with congenital heart disease who died due to cardiac arrythmia or sudden death while on risperidone.

The fifth cardiac case involved an 11 year old female who died of myocarditis one month after initiating risperidone therapy.

A sixth case involved a seven year old male who experienced QTc prolongation and died due to a heart attack after initiating therapy with risperidone.

The seventh case involved a 16 year old male with a family history of Protein S deficiency who experienced an upper respiratory infection and a presumed pulmonary embolism and died three months after initiating therapy with risperidone.

And the last two cardiac cases involve an 11 year old and a 16 year old on risperidone who died possibly due to left

ventricular hypertrophy.

The last eight death cases are summarized on this slide. Six of the eight cases involved a single report for an adverse event and n o patterns were identified. The cases include a 14 year old who had a viral infection and cardiorespiratory arrest prior to death and while on risperidone; a 14 and a 12 year old who died from suicide which is labeled association; a 13 year old on risperidone who had pneumonia, septicemia, congestive heart failure, and cardiac arrest and died; an eight year old with diabetes who had a hypoglycemic seizure and died while on risperidone; a six year old who died after an accidental ingestion of multiple medications, including risperidone; a five year old who died after a near drowning within three months of initiating risperidone therapy; and a one year old who died of suffocation after receiving her mother's risperidone.

Now, going back to the table

describing adverse events since marketing approval, for pediatric patients, there were 1,207 pediatric serious adverse event reports with 860 of these being U.S. cases. You will note that the definition of a serious adverse event that was used when identifying these cases is provided in the footnote.

Now, looking at the post exclusivity period for pediatric patients there were 131 serious adverse event report with 42 of these being U.S. reports.

Of the crude count, 131 pediatric serious adverse event reports identified during the post exclusivity period, 15 reports were excluded because they were duplicates. Of the 116 remaining unique pediatric cases, no new safety concerns were identified.

The safety reviewer gave particular attention to 35 cases involving labeled metabolic extrapyramidal and gynecomastia and hyperprolactinemia events to see if there was a qualitative or quantitative difference in

the reports for pediatric patients compared to adults.

Again, there are multiple sections in the drug labeling that are relevant to these selected serious adverse events. The warnings and precautions section of the drug labeling include subsections on hyperglycemia and diabetes mellitus, tardive dyskinesia, and hyperprolactinemia.

The adverse reaction section of the drug labeling mentions extrapyramidal symptoms and gynecomastia.

The 15 metabolic effect cases included cases of increased weight, diabetes mellitus, diabetic ketoacidosis and/or glycosuria. The 14 extrapyramidal cases included three tardive dyskinesia and 11 other extrapyramidal effect cases.

Lastly, there are four gynecomastia cases and two cases of hyperprolactinemia. Again, these events are consistent with current labeling.

This chart describes the various combinations of metabolic serious adverse events that were reported in pediatric patients. You will note that there were three groups of reports for diabetes alone or diabetes combined with another metabolic adverse event.

Of the 81 other pediatric serious adverse event cases during the post exclusivity period, the safety reviewer provided case counts according to the categories listed on this slide. There were 29 cases with labeled events and 53 cases with unlabeled events.

The drug labeling sections relevant to these other serious adverse events are the contraindications section, which includes hypersensitivity reactions, including angioedema, the warnings and precaution section, which includes cerebrovascular events, including stroke and transient ischemic attack, neuroleptic malignant

syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus with worsening glucose control, hyperprolactinemia, orthostatic hypotension, seizures, and suicide.

The adverse reaction section controlled clinical trials subsection mentions arrythmia, bradycardia, and tachycardia, leukopenia, anxiety, tremor, increased SGOT and SGPT, edema, and vomiting.

The post marketing experience subsection includes pulmonary embolism, cardiopulmonary arrest, thrombocytopenia, precocious puberty, angioedema, and pancreatitis, and the drug interaction section discusses how risperidone use can result in increased valproate plasma concentrations.

Of the 53 unlabeled events, no new safety concerns were identified. There were 30 non-therapeutic uses, including accidental exposures, intentional misuse or overdose and poisoning of food, 14 events that involved a single case report, and seven other adverse

event types reported in two to four cases.

Of note, the four cases of agitation during the switch from risperidone to methylphenidate are suggestive of off-label use for attention deficit hyperactivity disorder in which agitation can be part of that disorder.

Lastly, some of the remaining serious adverse events are consistent with schizophrenia or Bipolar I disorder, such as hallucinations, aggression, and self-injurious behavior. However, these events also can be seen in children and adolescents without these psychiatric diagnoses.

This completes the one-year post exclusivity adverse event reporting. The safety review did not reveal any new safety concerns for oral risperidone as the identified adverse events were qualitatively similar to those currently found in the product labeling and described in the adult population.

Therefore, FDA will continue its standard ongoing safety monitoring for oral risperidone. And then the question to you is: does the Advisory Committee concur?

And in closing I just would like to acknowledge the assistance I received in preparing for this presentation from numerous FDA staff in the Office of Surveillance and Epidemiology, the Division of Psychiatry Products, the Office of Clinical Pharmacology, the Office of Pediatric Therapeutics, and the Pediatric and Maternal Health staff.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

We're open to questions.

DR. RAKOWSKY: I have a question for Dr. Laughren, please.

We have a very nice report from Dr. Governale looking at the use of Risperdal over the last three years. In looking at the zero to 12 age range there's been basically a stable use in that age range, but the

percentage of change allowed to have the diagnosis or the coding of infantile autism, is that a code that will be used only for children less than two or is that a diagnosis code that you would use for any pediatric age?

In other words, the question is are we seeing more use in off label, in other words, less than five year olds, based on what we're seeing in the use data.

DR. LAUGHREN: Yes, I don't have an answer to that question. You know, in the division we're not the ones who collect the data on use. Maybe, Felicia, you could comment on that code infantile autism. Is that ICD-9?

DR. COLLINS: Actually I would need to defer to someone in the Office of Surveillance and Epidemiology.

CHAIRPERSON RAPPLEY: Please use the mic.

DR. BORDERS-HEMPHILL: I'm sorry. I'm Vicky Borders-Hemphill.

That is an ICD-9 code that we use, and we only looked at age groups zero to 12.

DR. RAKOWSKY: Would the infantile autism ICD-9 code basically be used for any child with autism less than 12, for example, and still be termed infantile autism, or is that just a subset of younger children of autism that this is being used for?

DR. BORDERS-HEMPHILL: Well, we also saw it as an ICD-9 code for 13 to 17 year olds as well.

DR. RAKOWSKY: So probably more of a broad range.

DR. BORDERS-HEMPHILL: Right.

DR. RAKOWSKY: Okay.

CHAIRPERSON RAPPLEY: Dr. Dure.

DR. DURE: Yes. I have a question for the psychiatry products group, too, because I'm a child neurologist, and I have a bias that extrapyramidal syndromes are really under-recognized with the use of these agents, and I would be concerned or my question is:

is enough being done because to try to at least educate people or do you have a concern about that on your panel?

It didn't take long for me to find out about diabetes mellitus and hyperprolactinemia with these agents a few years ago. I heard about that very quickly, but neuroleptic malignant syndromes, serotonin syndromes and akathisia, things like that. There is a lot of concern in the literature about people's ability to recognize this.

Do you feel like, in your Committee, do you feel like enough is being done to keep the public and the practitioners aware?

DR. LAUGHREN: Well, we think this drug is reasonably adequately labeled with regard to extrapyramidal side effect. You know, it's not really probably FDA's primary responsibility to go beyond that to educate the community.

I think it really falls more to the

various practice associations to educate their members, but you know, we're open to suggestions about what you think we might be able to do to further educate.

CHAIRPERSON RAPPLEY: Dr. Farrar.

DR. FARRAR: I would like to follow up on that because I agree. I think one of the things that I have seen is a lot of very hard to define movement disorders in kids who are being treated off label with this, and this is just my experience in the clinical setting, and I don't have any hard numbers to really say what that means.

And so I thought it was interesting that of the movement disorders, 11 of them were described as other extrapyramidal, and so it sounds like there's kind of this general tendency out there for people to have a hard time deciding what it is. These kids are not fitting really typical patterns it doesn't sound like.

Again, I'm not sure what other

studies need to be done.

One of the other things that I was interested in when I looked through this is that although from looking at the prescribing on page 125, yes, bipolar and schizophrenia are the most common diagnoses for which these drugs are prescribed, but all others is 99,000 or almost half of the use of this.

Again, you all can't set policy. You all can't tell doctors how to prescribe drugs, and so I think you're caught a little bit here, but these drugs are being used, and plus that's in the zero to 12 year group, and so just the data looks like there's a tremendous amount of off-label use of these drugs going on out there.

I'm not sure. I agree there's not much you can do with the label right now because qualitatively what you're seen in your reports and the data you have looks like what you talk about in the label, but I don't know. I'm not sure if we can make a recommendation

or what this Committee can do to try to encourage more study of these drugs, especially in children, because I think there's a lot of off label use and I think there are a lot of side effects that are not fitting into the normal categories very well.

CHAIRPERSON RAPPLEY: Dr. Goldstein.

DR. GOLDSTEIN: Again, this is not my area of expertise, but in reading through the data there clearly is a statement that there's a dose response effect regarding safety, and there's also repeatedly in the label that there is no control data to support long-term use either in schizophrenia, bipolar mania, or the irritability associated autistic indications.

So given that there are significant metabolic effects, CNS effects and cardiac effects, and especially the metabolic effects which one would assume would accrue over time, my questions are, not being a practicing

psychiatrist: what's the typical length of treatment? Do we have any data on the long-term use from the adverse event reporting? Is there any way to ferret that out? Is there a cumulative or is there the possibility that there's a cumulative dose effect?

And then my last question is that when you look at the label statements regarding extended periods, the statement under schizophrenia is different than that under bipolar mania and autistic. The statement for schizophrenia just cautions the physician who uses Risperdal for extended periods of time to periodically reevaluate the long-term usefulness, whereas the statements for bipolar mania and irritability associated with autistic disorder caution to reevaluate long-term risk and benefits.

DR. LAUGHREN: Well, in terms of the first question about long-term safety, it's very difficult to get good, systematic, long-term safety data in anyone, but in kids

in particular. The labeling describes the data that we have, and those are, you know, from open label extensions, and we give some descriptive numbers of what happens. You can't really get long-term control data. In other words, you couldn't do a year long placebo controlled trial and systematically look at the cumulative effects. You can only look at a cohort.

And those are suggestive that there are some cumulative effects, and we've reported that in the labeling, but you know, we agree that these drugs, this drug included among the atypicals, have metabolic burden. You know, they increase weight. They alter lipid profiles. They have effects on glucose, and we think that's important for prescribers to know, and we think the labeling, you know, clearly expresses that concern.

CHAIRPERSON RAPPLEY: Dr. Notterman, then Dr. Kosic, and we have two others in the wings.

DR. GOLDSTEIN: I'm sorry. Why is there a difference in the recommendations to the physician for schizophrenia as compared to the other two?

DR. LAUGHREN: Can you again say exactly what you're referring to?

DR. GOLDSTEIN: It's on page 152 of my booklet under schizophrenia, the last statement, the first paragraph at the top of the page. The physician who elects to use Risperdal for extended periods in adolescents with schizophrenia should periodically reevaluate the long-term usefulness of the drug for the individual patient.

DR. LAUGHREN: Okay.

DR. GOLDSTEIN: But then on page 153 and again on 154 under the bipolar and the autistic sections, the last paragraph on page 153 -- I'm sorry -- the second paragraph, the last sentence on page 153, it says, The physician who elects to use Risperdal for extended periods should periodically

reevaluate the long-term risks and benefits of the drug for the individual patient.

And that same sentence is used for the autistic. So my question is that it just looks like efficacy is being recommended for follow-up under schizophrenia, whereas efficacy and safety is being recommended for the other two conditions.

It just seems to be inconsistent.

DR. LAUGHREN: I'm sure that was inadvertent, you know. It certainly wasn't intended that one wouldn't look at both efficacy and safety long term. So it's something we can consider fixing.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: A review of the prescribing indications shows that there's a substantial amount of prescribing for ADD in the under 12 group, 16.8 percent in the latest dates. And I wonder if in light of some of the toxicities and adverse effects that you've

acknowledged are significant, the metabolic burden, we have given substantially enough weight to these adverse events in light of the off label indications for which the drug is being prescribed.

So by that I mean in balancing the benefit and risk of the drug and the burden of the drug, the balance seems clearly in favor when used for a disorder such as schizophrenia or another psychotic illness.

However, it doesn't seem to favor the use of this agent in certain unlabeled indications, in particular for ADD, and so I guess my question is whether some other action, for example, a notice to prescribers regarding the use in ADD is worth considering in the future.

DR. LAUGHREN: You know, it's hard to tease out from the data exactly what the drug is being prescribed for in kids with ADHD. I suspect what it is is being used for co-morbid either oppositional defined disorder

or conduct disorder since that's in child psychiatry probably the most widely used diagnosis. You can't really tease that out from these data.

But to your question about, you know, what can FDA do in terms of off label prescribing, again, you've heard this many times, but we don't regulate the practice of medicine. Once we put a drug out there, we can clearly say in the label what it is indicated for, you know, what the appropriate use is from our standpoint for those approved indications.

Again, we're open to suggestions, but it's not clear what you would want FDA to do to try and influence the way the drug is used in the community.

DR. NOTTERMAN: Well, I do agree that some of the use at least that I'm aware of is for oppositional defined disorder, but I think there's also substantial use for ADD without those characteristics.

And as for what I think FDA should consider, it is the evaluation of the adverse effects in light of the actual use of the drug, and in particular, to consider whether -- and it may be that there isn't and it may be that you're right and this is misleading coding, but to consider whether there is substantial use by practitioners for this indication in the context of a significant metabolic burden.

I also have one other question related to that, and that is whether or not there's data on QTc prolongation for this agent when used in monotherapy.

DR. LAUGHREN: If you look at the labeling under ECG, there were changes made on the basis of the new data that came out of these studies, which basically says that there weren't any important changes noted other than a slight increase in pulse rate.

DR. NOTTERMAN: So do you know if QTc was specifically included in that

surveillance?

DR. LAUGHREN: Well, ECGs were collected, but of course, this is in the context of a typical clinical trial rather than a thorough QT study. So, you know, it's true that you can't take quite as much away from that as you could from a thorough QT study, but this compound risperidone has been looked at a lot for QT, and it doesn't appear to have much of a signal.

DR. NOTTERMAN: Thanks.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: In looking at this drug compared to many of the drugs that we're going to review or have reviewed over the few years that I've been here, this is somewhat unique in that it's being used in -- 25 percent of its use has been in pediatrics. It's a drug that has many effects, some that are serious, and I would disagree with your assessment that the FDA is passive in this thing and what they can do.

My sense of reading this, there are some very serious signals and my read on the labeling is that it's inadequate to those signals that you've known about, we've known about, and it doesn't emphasize the life threatening side effects.

So for me when I read through this -- and, again, I don't use these drugs myself. So it's simply naive as I read through these things -- that I think it's inadequate in labeling for seizures in the sense that it doesn't include -- there are seizures and then there is -- epileptic that's leading to seizures and death. There's the metabolic effects where we talk about hypoglycemia and diabetes, but there's also diabetic ketoacidosis that's not emphasized. I'm not sure if that led to death.

And then the cardiac toxicities were reviewed and apparently they brought in a consultant to review that, and it ties somewhat into the QT studies, and I'm curious

about that, if you acquire the EKGs, why QT studies weren't -- or I don't know the results. Maybe they were done. I don't know what that impact was, but I'm curious as to what the consultant found and reviewed to see if there's additional things we need to monitor.

And then the final comment is on behalf of the sponsor, in the labeling when they talk about the long-term effects of Risperdal on growth and sexual maturation have not been fully evaluated, I find that lacking in the sense that we know it has profound impact on prolactin and other endocrine things that I believe should require them to study this in children who are undergoing sexual maturation.

DR. LAUGHREN: Well, I'm a little puzzled about your statement that labeling is inadequate with regard to some of these serious risks. These are all warning statements, very prominent warning statements.

You know, the statement on hyperglycemia talks about the possibility of ketoacidosis, although I must say that what you're dealing with are individual reports, spontaneous reports of children developing what in many of these cases of ketoacidosis is Type 1 diabetes.

The kind of diabetes that we expect to see with a drug like an atypical antipsychotic which induces weight gain and lipid changes and hyperglycemia is Type 2 diabetes. The end stage of that would be hyperosmolar coma. You see ketoacidosis with Type 1 diabetes.

There's no particular reason to believe that this drug induces Type 1 diabetes. More likely what you're seeing are, you know, the natural occurrence in this age group where it's the peak onset of Type 1 diabetes.

So again, I'm puzzled by --

CHAIRPERSON RAPPLEY: Excuse me.

To that point, I believe I've read in the material that you've compiled for us that there have been spontaneous reports of hyperosmolar ketoacidosis, and that, in fact, people do recognize and accept the risk of Type 2 diabetes with the metabolic syndrome, have been part of the metabolic syndrome.

So I wouldn't want to diminish that as a risk factor because children are also developing Type 1.

DR. LAUGHREN: I totally agree, but again, I'm anxious to hear suggestions about, you know, what more we can do in labeling. It's already very prominently labeled. The same with seizures.

CHAIRPERSON RAPPLEY: I'd like to allow Dr. Rosenthal, Dr. Cnaan and Ms. Celento to speak. Dr. Rosenthal.

DR. ROSENTHAL: Thank you.

I actually am just reflecting on the very high incidence of hyperprolactinemia in the pediatric population. I'm sitting here

wondering what is the effect of that over the years in which these medications are going to be used.

I think the label effectively calls out that high occurrence, but I think my question may relate somewhat to Dr. Kocis' question, and that is if these medications are used to a significant degree in the pediatric population, and there is information regarding the effects of the medication on the neural endocrine access. Is it reasonable to ask the question of what is the long-term effect on growth and development in these areas.

DR. LAUGHREN: That's always a good question to ask. The difficulty, of course, is in trying to figure out how you're going to get an answer to that question. How are you going to mount a trial that allows you to follow a cohort for the years and years that you would need to to gather that information, especially if you wanted to have some kind of a control? It's a challenge.

DR. ROSENTHAL: So I guess I'm not asking the agency to design the study, but I'm wondering whether there aren't some mechanisms even through the labeling process where particular attention can be drawn to this point, which might then stimulate research in this area.

You know, the we don't think of the label as being used in this way, but I'm thinking outside the box, and maybe if particular attention is drawn to the very high occurrence of hyperprolactinemia in the label, that will raise enough eyebrows that the studies will get done.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: In the interest of time, my question mostly mimics Dr. Notterman's question. I am very concerned when I look at the second most prescribed indication being ADHD, as was pointed out in Slide No. 5, and the cumulative effect of everything that everybody has said here. It

is not about the labeling, but if there is anything that the agency can do to decrease, at least, off label use for more mild indication, I think I would greatly appreciate it.

CHAIRPERSON RAPPLEY: Ms. Celento.

MS. CELENTO: I second Dr. Cnaan's comments, and really the comments of everyone else. And I will say that, you know, maybe it's the Google generation and people stopped reading at page one. I don't feel that the metabolic indications or the metabolic effects are highlighted in the label, and I realize there's a standard format for the label, but I don't think those concerns are really broadly raised here for the parent of a pediatric patient.

And, again, some of these drugs are being -- this drug is being used maybe for indications that are off label, and there might be other options.

DR. LAUGHREN: Yes, with regard to

the metabolic issue, I can say that there's a review ongoing within the agency right now looking extensively at the metabolic effects for all of the atypicals. We've pretty much completed our review for the other drug that you're going to talk about here this morning, Zyprexa, and the labeling for that drug, I think, better reflects the metabolic risks.

You know, we expect over the next couple of years to improve the highlighting of the metabolic profile for this drug and the other atypicals, but that review is ongoing.

CHAIRPERSON RAPPLEY: I'd like to make an observation that of the 31 deaths that were described here by my reckoning, 11 of those were associated with off label use. Eleven of those had no diagnosis clearly associated with use, at least in the information available, and six were associated with on label use.

It's also an observation, and I know there's not a really rigorous -- there's

no evidence to be gleaned, but just a signal perhaps. Nine of these deaths were associated with SSRI concomitant use, and 12, including that nine, were associated with antidepressants.

So I wonder if there isn't something that we should be looking at there.

I do think we have an avenue perhaps around our shared concern about off label use and the rapid increase in use. You described to us a ten percent increase in use for children zero to 17 within the last year. What was presented to the Best Pharmaceuticals Committee -- am I saying that right? What's the name of that group that we did in June? No, no, the Best Pharmaceuticals Act for Children -- the Best Pharmaceuticals Children's Act. That committee met in June and risperidone was one of their items of concern, was one of their medications that they asked to be reviewed, and I was assigned to review that as a participant in that

committee.

There was information presented there that based on data in seven states in both Medicaid utilization and commercial insurance utilization, that risperidone, in particular, was used by more than 16 or had a prevalence of more than 16 among Medicaid youth and a prevalence of approximately four among those in commercial insurance.

Now, that data comes from 2001 and 2004. So we all have a sense that this increase that you describe over the last year has actually been cumulative since 2000, those of us in practice.

So I think we share a concern about off label use and a very rapid increase in use of this medication. I say this with the caveat that I think it's a very effective medication, and it is a very powerful medication. I use the word powerful because it has brought an improved quality of life to many, many children who could not experience

that previously.

But because of that, it lends itself to off label use, and I think that perhaps we've not in the past viewed the label or the agency as a tool to influence practice, but we do have a request from the Best Pharmaceuticals for Children's Act to recommend --

DR. MURPHY: This is an NIH committee.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: This is the NIH committee, just so everybody is on the same page as Marsha, that looks at the off -- well, actually they're not just looking at --

CHAIRPERSON RAPPLEY: They're asking what should be future research.

DR. MURPHY: Not looking just off patent, right.

CHAIRPERSON RAPPLEY: Where should research for children and pharmaceuticals focus?

DR. MURPHY: Right.

CHAIRPERSON RAPPLEY: And I think we could take the concern of this Committee to them. We could convey to them that we have a concern about off label use; that we have a concern about long-term effects; and that we have a concern about extrapyramidal effects in this very widely used and increasingly used medication.

And that could then be added to the many people who spoke about the importance of studying this particular medication and this particular class of medications in children.

DR. MURPHY: And I think in that situation you might want to articulate at the end here what are the groups that you think, because I've heard a number, you know, of the proactinemia, the endocrine effects, the, you know, long-term effects, maybe the differences in the metabolic effects going through puberty.

I mean, those are some of the

things that I've heard you say, and, Tom, I think what they're saying is they recognize the agency doesn't really have a mechanism to get those things done unless, you know, this probably came in with a supplement for something that would somehow avail itself to that, but otherwise they're trying to search for other ways to get this done.

I think though the one other thing that we need to make sure, and people have been careful about this, is that your concern -- and we've seen this before with other products -- is that the large off label use in a population that has not been documented to receive any benefit from this product is the concern fundamentally I think I'm hearing expressed.

And I don't know if there's a way. Let me just put it this way. We would not go and put in a label, Don't use this for ADHD. I mean, we can't start doing that. It's not what we would do.

If there were some way of enhancing, you know, the do not use any other way -- I can't think of, Tom -- then you already put in here. You've said if you're going to use it long term, you really need to reassess it and they'll fix the difference that was brought up for that, but don't use it.

I guess the question I'm hearing is is there a way to say if you're using it for anything other than the indications, you need to somehow reassess what you're doing. You know, I don't know if --

CHAIRPERSON RAPPLEY: Can I suggest a sentence and then you tell me if it would be reasonable or not? You know, I'm not asking the agency to step outside its bounds.

But would it be reasonable to say caution should be taken and careful consideration of risk of known side effects with perceived benefit in any off label use? Something like that on that first page where

it's --

DR. MURPHY: Well, I'm sure I can tell you right now --

CHAIRPERSON RAPPLEY: That won't work?

DR. MURPHY: -- the lawyers would not let us do that, and they always get upset when we physicians start to practice law. But, I mean, there's no way they would allow us to put something about off label use.

CHAIRPERSON RAPPLEY: Well, I guess we do have other ways that we can bring to light concerns about off label use of any medication and the kind of increasing prevalence that we see with this one.

We do have other people who would like to comment on this. Are these new comments or are they reinforcing?

DR. DURE: Well, I was asked for any suggestions, and that was a while ago, but I mean, under the use in special populations, the only movement disorder you mentioned is

tardive dyskinesia, which almost never gets described, yet 20 percent of children in the pediatric studies have some combination of a movement disorder, distonia, akethisia, et cetera.

I mean, I would echo that that's inadequate because they can be serious side effects, and I would also take issue. I mean, again, I've heard this, that the FDA does not regulate the practice of medicine, and I'm not suggesting a black box warning, but that is what is done.

And so I think this Committee is a little frustrated because we are trying to figure out a way that we can accommodate this concern of ours, and it's a well founded concern that we have.

CHAIRPERSON RAPPLEY: We do need to take a vote on this question. Can you put the question back up on the screen?

DR. MURPHY: And, Marsha, at the end would you summarize the recommendations of

the Committee because that's the thing we're supposed to get from this Committee.

CHAIRPERSON RAPPLEY: Yes, I will try to do so, and you all can monitor that.

Dr. Notterman is very much wanting to make another comment. So one last comment.

DR. NOTTERMAN: I just wanted to ask a process question. It seems to me that part of the concern is that what actually is subsumed under or within the penumbrae of attentional deficit disorder and other emotional diseases of childhood and all others, what's subsumed under that makes many of us uncomfortable. It may be that there's a large nucleus of labeled indications or at least serious illness that's subsumed there, and that would at least make me more comfortable in evaluating the serious nature of these side effects, particularly the extrapyramidal reactions and metabolic burden and perhaps the cardiac toxicity.

So is it possible for the agency to

learn more about the actual prescribing practices over the next year or so and then report back to us and other committees?

CHAIRPERSON RAPPLEY: So you would be considering followup information would be important to the Committee.

DR. NOTTERMAN: On the actual indications with more precision perhaps in a prospective way.

DR. LAUGHREN: We can go back to our colleagues in Office of Surveillance and Epidemiology, the people who collect data on use, and see if they can get more precise about the uses and the numbers and so forth.

DR. MURPHY: I think that's actually a very helpful way to try to move forward, is to better understand that population, and you heard yesterday about the new databases. Some of them they really have not delved into to understand their functionality as well, and so we can give them an opportunity, as they like to say here, to

maybe try out some of these new systems and databases.

CHAIRPERSON RAPPLEY: So the Committee then needs to vote on the question that one year post exclusivity was completed, and the safety review did not reveal any new safety concerns; that the FDA will continue its standard ongoing safety monitoring for oral risperidone.

So we need to vote on that question, and then I will summarize recommendations from the Committee and you can edit my summary.

So the vote will be the FDA will continue its standard ongoing safety monitoring for oral risperidone. How many on the Committee support that?

(No response.)

CHAIRPERSON RAPPLEY: So I am not seeing any hands raised.

Yes.

MS. CELENTO: I think the challenge

is that, you know, there are some of us that are thinking, and more, and so how do you answer yes to this question?

CHAIRPERSON RAPPLEY: So would you like me to summarize our recommendations first before we vote? Okay.

So a summary then of the recommendations that have arisen from our discussion today is that, one, the Committee would like followup information regarding actual use in light of concern for extensive and rapidly increasing off label use of risperidone.

Number two, that we would express concern and like to see further information and further encouragement of investigation of long-term effects of this medication, including the metabolic syndrome, the other endocrine effects, in particular, hyperprolactinemia, effects on growth and sexual maturation;

That we would also like to see

encouragement of further investigation and whatever followup information can be gleaned over the next period of time about extrapyramidal side effects.

Additions to that summary?

DR. MURPHY: I just want to make sure that when you said the followup for the actual use, you want more than a -- I think we need a little more specificity on that because I want to make sure that it is addressing the issue that Dr. Notterman is definite the ADHD population, having more information about that population.

CHAIRPERSON RAPPLEY: So we would like more information about how the medication is actually used and for what indications it is prescribed in as great detail or specificity as you're able to glean from your data sets.

DR. FARRAR: I would like to add that, you know, we're going to have this same discussion in just a couple of minutes.

CHAIRPERSON RAPPLEY: Well, that's correct.

DR. FARRAR: And we'll have it probably every time, and there's a bunch of these drugs, and they're starting to come out. Is there a mechanism to do a class of drugs study where you would look at this whole class of drugs with these questions in mind?

Because we're going to be asking this question over and over again. Movement disorders, metabolic diseases have all been identified with, I think, all of these drugs. We're seeing it a lot with risperidone now just because it was the first to market and we have the most data on it, but as time goes on you're going to see it over and over again with a lot of other drugs, and I don't know if there's a mechanism for doing that or if that needs to be considered as part of the recommendation.

CHAIRPERSON RAPPLEY: So correct me if I'm wrong, but I think that would be a

recommendation that could go to the Best Pharmaceuticals for Children's Act Committee at NIH to look at investigating a class of medications as a priority for the nation.

But for us at the FDA, we have to go product by product; is that correct?

DR. MURPHY: Well, you know, I think that's an efficient way to approach it because you do know you're right, Marsha, that we do have to go product by product. But when you do that, you can say we're concerned about the class, and that Lisa and Dr. Rodriguez who works with the Committee also will make sure that we bring back this as an issue to that group, the NIH group, yes.

CHAIRPERSON RAPPLEY: Okay. So then I will ask Dr. Pena to read the summary that I just gave and so that we can think about it again before we vote.

DR. PENA: Okay. So PAC would like followup on extensive off label use. It would like further information on long-term effects

for this medication on metabolic syndrome growth, sexual maturation; would like a followup report on extrapyramidal side effects; would like more information on its use in prescribing information; and recommends potentially a class of medications review at a followup meeting.

CHAIRPERSON RAPPLEY: And I would add specifically hypoprolactinemia under the area where you say sexual maturation and growth.

Yes.

DR. KOCIS: One other thing. Yesterday we learned about some of the new databases that allow for looking not only at single drug use but combination drug use. I don't know if those databases are up and running in such a fashion that we can also glean some look at concomitant multiples. You've heard SSRIs, antidepressives, even some of the hyperglycemic agents and stuff.

But I think that would also be an

interesting question.

CHAIRPERSON RAPPLEY: Dr. Pena just added that. So thank you.

So given that that will be recommendations of this Committee to the agency, we now also need to vote on the question of FDA. So the statement is FDA will continue its standard ongoing safety monitoring for oral risperidone.

I'm sorry?

And the additional items that we described in that summary, yes. Discussion?

DR. NOTTERMAN: I'm not sure. Perhaps you can enlighten me. The continuing of standard ongoing safety and taking under consideration these extensive recommendations are compatible statements

DR. MURPHY: I guess I'm sitting here thinking I think you said no. I think you've said we think there are additional pieces of information that we would like to have, and what we have to --

CHAIRPERSON RAPPLEY: Excuse me. How about in addition to standard ongoing safety monitoring?

DR. GOLDSTEIN: Or you could just say you expand its standard ongoing safety monitoring for oral risperidone and then to include the following.

DR. MURPHY: Well, what this is saying is that there's really nothing more that you want. Okay. That's what this is saying.

CHAIRPERSON RAPPLEY: And we don't agree with that. That's correct.

DR. MURPHY: I know you're not agreeing with that statement.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: Okay. You're saying that we're not finished with looking at the adverse effects of these products, particularly this product, in the pediatric population. We have additional concerns. We understand the agency can't require some of