for children receiving celecoxib off-label.

Now, to consider the safety that would be expected for celecoxib's use in children, it's important to also look at the risks that are known to be associated with celecoxib and with the non-steroidal class in general.

First considering the known risks, the adverse events that are associated with the NSAID class include cardiovascular toxicity, GI toxicity, fluid retention, edema, renal toxicity, hepatic enzyme elevation, and bronchospasm in patients with aspirin-sensitive asthma.

In addition, serious skin reactions have been seen with celecoxib, including Stevens Johnson Syndrome.

The pediatric experience in Study 195 showed one case of liver enzyme elevations and one case of severe asthma. Overall, these adverse events were not seen at a rate clearly higher than that which was seen with naproxen.

Turning next to the risk of GI bleeding, I'm sure you're all aware that the COX-2

selective class of NSAIDs was originally developed with the hope that it would reduce the life-threatening GI bleeds that were seen with non-selective NSAIDs.

Well, celecoxib has been shown to reduce GI ulcers endoscopically. The incidence of clinical GI bleeds has not been shown to be reduced.

In children, GI bleeding is an uncommon adverse event with non-steroidals and no GI bleeds were seen in Pediatric Study 195 with celecoxib.

Turning to cardiovascular risks, I'm sure you're all aware of the attention that this has received in recent years. Data indicate an increased risk of cardiovascular thromboembolic events, in particular myocardial infarction, in adults treated long term with COX selective NSAIDs, including celecoxib.

However, the risk of cardiovascular events with non-selective NSAIDs has not been clearly shown to be less than with COX-2 selective

NSAIDs.

Given that it is primarily adults who are at risk for cardiovascular thromboembolic events, such events were not expected in the celecoxib trial and indeed none were observed. However, the long-term risk for children treated with celecoxib is unknown.

Cardiovascular risk is a potential concern in children with JRA in view of the risk of accelerated atherosclerosis associated with inflammatory rheumatic disease in adults, such as is seen with lupus and rheumatoid arthritis, and in addition, there's a recognition that increasing numbers of children have other risk factors for cardiovascular disease, such as obesity, hypertension, hyperlipidemia, and Type 2 diabetes.

So, in summary, the safety that was available at the time of the initial approval, overall the risk of adverse events was similar in children receiving celecoxib as those receiving naproxen, and overall the safety profile in Study 195 was similar to that which was known to be

associated with the NSAID class of drugs.

So, considerations in assessing the overall risk-benefit for celecoxib in children. It's important to consider the observed safety profile of celecoxib in JRA based on the limited information from the randomized trial, to also consider the known risks of NSAIDs in this patient population, and to consider the potential long-term risks based on the knowledge gained from studies in adults.

In the end, it was decided that the risk-benefit profile for celecoxib in treating children with JRA was favorable. However, it was felt that there was not complete information about safety and the company agreed to the postmarketing commitments shown on this slide.

They agreed to do a postmarketing safety study in children with JRA which would include assessment of GI events. They agreed to conduct a prospective observational registry, and they agreed to do pharmacovigilance activities focusing on the adverse events of interest.

Thank you.

DR. RAPPLEY: Thank you, Dr. Siegel.

I think for organizational reasons, we'll break for lunch now and then come back with Dr. Sachs and the sponsor, and it is after Dr. Sachs's presentation that specific questions will be put to the committee.

So, if we convene back here at 1 o'clock and we will apologize for the delay in the public hearing for those of you who may be here for that purpose, but we will be having our public hearing following the discussion of celecoxib.

So, back at 1. Thank you.

(Whereupon, the meeting recessed at 11:56 a.m. and reconvened at 1:03 p.m.)

AFTERNOON SESSION

1:03 p.m.

DR. RAPPLEY: I would like to at this point in time ask for intent to speak at the public hearing. So once again, I'll just repeat that, if there's anyone who intends to speak to the committee at the open public hearing portion, yes? Okay. We're not going to start that yet but just to note that you do intend to speak. Okay. So, we have one speaker and will you need the speaker's name?

So, we're not going to start that until after our celecoxib discussion, but we just wanted to know how to schedule that.

DR. MURPHY: Let's go ahead. Let's go ahead. Marsha, I think we should because we're far enough behind schedule, I think we better.

DR. RAPPLEY: Fine. That's fine. Thank you.

Open Public Hearing

DR. SCHWEIKERT: Thank you very much. I'm Alfred Schweikert. I'm Director of Global Regulatory Affairs for Baxter Healthcare.

DR. RAPPLEY: Okay. We need to have a pause just for a moment, and we have to read a statement for the record.

DR. SCHWEIKERT: I'm sorry, I couldn't hear you.

DR. RAPPLEY: And then we will turn the mic over to you.

DR. SCHWEIKERT: Okay.

DR. RAPPLEY: The statement is both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such

transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsors, their products, and, if known, their direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you.

DR. SCHWEIKERT: Thank you. And again, my name is Alfred Schweikert, and I'm Director of Global Regulatory Affairs for Baxter Healthcare. Two of our products were discussed this morning, Brevibloc and Suprane.

I just want to tell the committee that along with the committee and our esteemed members here, safety for patients and our customers is our primary concern at all times.

I have two clarifications that I would like to ask of the committee. One is that when the discussion for Suprane was going back and forth, it appeared to me in the audience that the committee recommended to continue routine monitoring but the term "cardiac arrest" never came up again.

So, from where I was sitting, it appears that we were going to continue routine monitoring of Suprane and that there would be further discussions regarding any label changes but that an imminent label change for cardiac

arrest would occur some years down the road when more data was available, is that correct?

DR. RAPPLEY: Is there a second thing you want us to clarify?

DR. SCHWEIKERT: Okay. And the second thing I wanted to clarify is that Baxter Healthcare has many professionals in the anesthesiology business, including our own medical director which is a member of the FDA Anesthesiology Board and Committee.

I would like to know what would be the process that Baxter would enter into these discussions regarding the label of its product and the recommendations before anything is determined by the committee and what is the process for us to be part of that?

Thank you.

DR. RAPPLEY: Okay. So, two questions you have for the committee directly relevant to your product is a question about whether we have recommended a label change immediately around the cardiac arrest, including

cardiac arrest as an adverse event or if we recommend considering label change after further monitoring, at which time the agency will present to us any additional data and make recommendation.

So, given that label change is not an easy thing to accomplish, I would propose that we make consideration of the label change at the time that we have more information, the information that we've requested.

Any discussion or sentiment otherwise on the committee?

DR. MURPHY: I was going to say, so far what I've written down was that the first question, before we got into the extensive discussion where we changed the monitoring, was did the revision of the label to include cardiac arrest, and at that time, I'd written down that there was unanimous opinion to include cardiac arrest.

DR. RAPPLEY: We did vote that unanimously.

DR. MURPHY: Then we got into the

discussion of the monitoring and so the question is does the committee now wish to delay that label change or do you want the label change anyway and then come back with the monitoring?

So, thank you for the clarification because otherwise I had taken it that you did want the label change for the cardiac arrest, but you wanted us to monitor as far as the other issues that we discussed.

So, if you -- we probably need to ask that question again, the first question again.

DR. RAPPLEY: Okay. So, then let's try to format the question. How many people on the committee would support an immediate label change to include cardiac arrest as an adverse event, in addition to other recommendations we also made?

You need to ask a clarifying question, Dr. Newman?

DR. NEWMAN: So, just to clarify, these other things would be changing the indications? Is that what you're saying, that

that would happen sooner?

DR. RAPPLEY: Well, we will have to talk about those after. I mean, the question --

DR. NEWMAN: I think everyone had already agreed to add the labeling for cardiac arrest.

DR. RAPPLEY: I'm sorry?

DR. NEWMAN: I think everyone had already agreed to add the labeling about cardiac arrest immediately.

DR. RAPPLEY: Right. We voted on that and we're unanimous.

The question is do we do that now and so we ask them to go out now and make a label change and then perhaps again a year from now go out and make another label change or do we delay label change until we have more information?

DR. NEWMAN: So, --

DR. RAPPLEY: So, the question before us is do we ask them to now make a label change?

DR. NEWMAN: But for cardiac arrest, you mean?

DR. RAPPLEY: Yes.

DR. NEWMAN: Okay. I thought we'd make the cardiac -- is it just making cardiac arrest label change and then make another label change about indications after it's been discussed?

DR. MURPHY: I think, Tom, the question really is did the subsequent conversation in some way negate the first vote. That's all we're trying to clarify, and then we'll get to the second question which I will answer right now.

The agency doesn't do labeling changes, as you know, on its own, and we would obviously be in conversations with the sponsor about that addition to adding cardiac arrest. I mean, it is a big deal for them because now they have to produce new labels, but if the, again, committee thinks it's important to have it in now, then we'll go into negotiations to have it in now, but we're trying to clarify and make sure that that's what you meant since we did the first vote and then we had the extensive discussion.

DR. RAPPLEY: Dr. Daum?

DR. DAUM: So, I'm one of the people obviously that was unanimously in favor of adding cardiac arrest, and I'm also one of the three minority people who favored routine monitoring.

So, to explain myself, I think that in the interests of compiling a laundry list of these things happened without causality implied necessarily, I was in favor of adding it as everyone else here was.

I also did not think that we would benefit from really close additional monitoring because we knew a lot of stuff about this drug. So, I think routine monitoring would have been fine.

So, I think that we thought collectively and unanimously that it should be added. Whether it's an urgent addition or could await additional information is another question and I don't think we considered that.

DR. MURPHY: So, I thought you just took another vote and everybody raised their hand

again. So, they still agree. So, could we just verify that because Carlos needs to verify who voted yes again. That's what we need to do at this point.

DR. RAPPLEY: In fact, Dr. Daum, that was the exact question that I tried to articulate and that is, does the committee -- will the committee please indicate who is in favor of asking the sponsor to make a label change at this point in time to include cardiac arrest as an adverse event? Who is in favor of that?

(Show of hands.)

DR. RAPPLEY: Who is opposed?

(No response.)

DR. RAPPLEY: Abstention?

(Show of hands.)

DR. RAPPLEY: Okay. Thank you. So that is -- Carlos will give us the exact number with one abstention.

DR. PENA: Thirteen in favor and one abstention.

DR. RAPPLEY: So, thank you for

asking us to clarify that, and are you clear about the response to your second request for clarification?

DR. SCHWEIKERT: If I can have it stated again?

DR. MURPHY: The agency, of course, will be in contact with the sponsor to talk about the recommendations from the committee for the immediate change.

DR. SCHWEIKERT: Is there a typical time frame for that? Sixty days?

DR. MURPHY: I would never try to predict the division's work. We will go back and give them the recommendation and they will have to put together, you know, a letter to you all.

DR. SCHWEIKERT: Okay.

DR. MURPHY: So, they will probably call you, but I would not want to prescribe their work for them. They would not like that.

DR. SCHWEIKERT: Okay.

DR. MURPHY: But it's, as you know, typical that they would do this immediately

afterwards. Immediately in government-speak, it's going to be at least a couple weeks.

DR. SCHWEIKERT: Okay. Thank you for your time.

DR. RAPPLEY: Thank you. And that concludes our open public hearing and we'd like to proceed now with the discussion of the celecoxib -- oh, I'm sorry. No, I'm right. I'm sorry. We have awards to give. We have awards, yes.

DR. MURPHY: You guys have been so vigorously talkative today that we wanted to make sure that we got the awards in in case we ran late. So, I do want to do that.

Okay. We have -- we're losing, as I said, almost the left-hand side of the table here and we really do recognize how much work individual members put into coming here and reading all this material and providing their opinions and so Dr. Bier, we'd appreciate it very much if you would come up and please accept this plaque from the Food and Drug Administration for your work and contributions to the FDA. We really

appreciate it. Thank you very much.

(Applause.)

DR. MURPHY: And Dr. Daum, we would also appreciate it if you would come up and accept this plaque from the Food and Drug Administration and we already asked you to continue your work in some way. So, just because we give you a plaque doesn't mean that we're going to leave you alone. I have to make that quite clear.

DR. DAUM: Thank you.

DR. MURPHY: Thank you very much.

(Applause.)

DR. MURPHY: Dr. Garofalo, it just seems like you and Sam have been with us for so long, this is really sad to see you go, and I want to thank you so much for your work and the extra pediatric neurology expertise, too, that you provided, besides being the industry representative. Thank you very much.

(Applause.)

DR. MURPHY: And Dr. Newman, it won't be the same without you. So, please accept this

plaque from us and thank you very much for your participation on the committee.

DR. NEWMAN: Thank you.

(Applause.)

DR. MURPHY: Okay. And Dr. Fant doesn't have a second plaque because we already gave it to him and as I said, we sometimes just won't let go, but now we totally have to, Dr. Fant, but we very much appreciate your continuing work with us, despite the fact that we gave you a plaque and told you it was all over with before. You know never to really believe everything we tell you. So, thank you very much, everybody.

(Applause.)

DR. RAPPLEY: Dr. Newman has asked me to clarify the second recommendation around Suprane and that is, does the agency understand the recommendation from the committee regarding the question of how we judge when we have enough information to make another change about recommendation and indication for Suprane?

Could the agency restate how you

understood that recommendation from the committee?

DR. MURPHY: What we understood is that we are going to continue to monitor the situation as far as adverse event reports and we will be back to the committee within one to two years, depending on the level, and I say that because we seldom go much beyond two years before we come back to the committee, depending on the level of adverse events that we see.

So that if we saw something that was indicative of an increasing rate of reporting or some particular cases we thought were more concerning, we would come back sooner than later is all I'm trying to say.

At that meeting, when we come back, which is the continued monitoring, not the routine monitoring that we will have, we will also discuss with the committee whether the division has any additional thoughts on the labeling and we were going to discuss and provide input to the committee on the risk-benefits at that time of the indications that were in the label.

DR. RAPPLEY: Okay. So now you're at a decision point. You either accept that the agency takes this recommendation as so stated from this committee or I call another vote about whether or not we should take this -- accept this recommendation.

I don't -- I have to say that I don't believe it's our charge to revisit whether or not this medication is indicated for the use as described in the label. It is our charge to let the agency know if we think that needs to be reconsidered, but we are not the experts nor do we have the information at hand that we could diligently say we've digested this and give you a thoughtful recommendation about contraindication, not approved or not recommended.

Yes, Dr. Newman?

DR. NEWMAN: Sorry. I just wanted to clarify because what Dr. Murphy said was that there was a minority who felt that maybe the labeling should be changed and the indications, and the vote, you know, where there were three

opposed, that was a vote about whether to do continued monitoring or not, and I guess it wasn't -- I just -- maybe that is a minority vote.

I think it wasn't clear when people were voting on that that they were voting that there wasn't enough information now to indicate in the indications that this should be a second line drug. That's all.

I just -- I don't think that that was -- maybe people who voted for continued monitoring might also have already felt that we know enough now from that randomized trial to say that, yes, this drug is less safe and the indications should be limited now, and I just -- I don't think that was clear when we took that vote.

So, I'm just hoping to get that to be clear.

DR. RAPPLEY: So, would you put another recommendation out that we should vote on?

DR. NEWMAN: The vote would be do we feel like the indication -- we have enough information now to ask them to relook at the

indications to indicate that this should be a second line drug because its safety profile is worse in children.

DR. RAPPLEY: So that is what you described to us and we will now take that as a further clarity of the recommendations that we've made, that we -- this committee makes a recommendation to the agency that they examine the risk-benefit ratio of this medication after they get information --

DR. MURPHY: After we get information. Okay.

DR. RAPPLEY: -- through the further monitoring.

Is this committee -- no? That's wrong?

DR. NEWMAN: No. Again, I don't think the further monitoring is going to help that much. I think we know enough from the randomized trial to know the drug is less safe, the further monitoring is not going to tell us much more, and I'm going to see whether I'm a minority or whether

other people feel the same way.

DR. RAPPLEY: Okay. I didn't -- I misunderstood then. That's a different question.

So, the question then before the committee is do we think that the agency -- do we recommend that the agency consider this question about risk-benefit after further monitoring or do we ask them to consider this question at this point in time?

So, how many people on this committee recommend to the agency that they consider this question after further monitoring?

(Show of hands.)

DR. RAPPLEY: Put your hands up higher so we can note how many. Did you have your hand up, Dr. Cnaan? Yes, you did.

And so those who are opposed to asking them to reconsider after further monitoring?

DR. NEWMAN: Or in favor of them changing it now. We have enough information. We want them to change it now.

DR. RAPPLEY: I didn't formulate the question well.

So, who is in support of asking them to take the question, consider the question now?

(Show of hands.)

DR. PENA: I have a count of eight. So, there's still three.

DR. RAPPLEY: Are there abstentions?

DR. MURPHY: What was the first vote? It was eight for the first -- eight for the second. What was the first?

DR. PENA: Three.

DR. RAPPLEY: Dr. Fant?

DR. FANT: Yes, I guess the question, you know, that I have is, is it within our purview to, for the labeling, to dictate practice in the sense of saying this should be a second line drug?

I mean, the way I tend to think of things like that is that's more within the realm of the anesthesiologists that are practicing to determine. You know, the labeling basically tells you what the drug does and doesn't do and then

it's up to the people who use the drug, you know, to determine the best practice in a specific situation.

So, you know, if the end game of our discussion now is to change labeling so that it reflects a designation of first line, second line, third line, I'm not sure that that's an appropriate conversation we should be having, unless there's something I don't understand.

DR. RAPPLEY: Well, I think the motion that we've voted on or the recommendation we voted on was to ask the agency to consider that and to do that with the process that they usually engage the true content experts around that.

DR. FANT: To consider making a recommendation regarding?

DR. MURPHY: And I can tell you that you've asked us to consider it and we would, but it would be usual that we would not go in and make that indication without bringing it to a committee and having a full discussion.

So, you know, I just need to make

sure the committee's aware of that because to be able to weigh the risk-benefits, you need to have a full discussion and so you're making a labeling change recommendation without having that full discussion because you think you have enough information, which is your right to express a concern, but I'm just saying it's fine to express your concern, but you're right to have that labeling change, we would have to -- we would usually, unless it was so apparent and what you heard from the division, they didn't think it was, they think there's another side to this discussion that wasn't heard today, that they would have a further whole discussion of the risks and benefits before they would change the label.

So, but it's fine to take the recommendation back to them, if that's what the committee wants to send the message back to -- if you want to send the message back to them.

DR. RAPPLEY: I believe that I formulated the recommendation as asking you to consider it in whatever your usual process would

be. Do you all agree? We are not recommending specific language to be included in there.

DR. MURPHY: Right. Exactly. You aren't and so I'm just making it clear. It could be that they would take the consideration and say, oh, we agree and we have wording we want. It could be that they're going to say, gee, we think there's enough other opinion that we, you know, come out in this the way we have already. We need to bring in the other opinion to look at it. They could do that, and they could -- or they could have another advisory committee before they change the label again.

So, I'm just trying to lay out the possibilities that would happen.

DR. RAPPLEY: So, to revisit that vote, we had three people who were -- can you repeat the vote again, Carlos?

DR. PENA: We had three individuals voting for continuing monitoring. There was nine not in favor. I do need clarification from Drs. Notterman and Sable on their position.

DR. NOTTERMAN: As the recommendation was reformulated by Dianne, then I vote in favor.

DR. SABLE: I would second that. I think we were -- some of the questions we were answering before lunch is a little different than we're answering now. I think that we're in favor of whatever process it would take to consider changing the labeling.

DR. MURPHY: Okay. So, Carlos, what I have now is you have three members who would wish to continue to wait to have additional information and wait till we come back to consider the changing of the labeling with that discussion that would be there, and then eight or nine or how many?

DR. PENA: No, it's five and nine. It's five in favor, nine not in favor.

DR. MURPHY: Okay.

DR. RAPPLEY: No, I don't think so, Carlos. So, I think we just really have become confused.

DR. MURPHY: I think we've got the

message.

DR. RAPPLEY: We need to continue to formulate the question.

DR. MURPHY: It's not unanimous.

DR. RAPPLEY: That's the problem.

DR. MURPHY: And there is an opinion by the committee, by some people, that we need to consider now potentially changing the label to indicate that this product should be used and we don't put first and second line on the label.

So that's just another thing to let you know. So we have to have the wording for that, but it would discourage more the use of this product fundamentally. There's a recommendation for that now by a majority of the committee and that there are others who feel that it's adequate to wait until we come back with additional monitoring.

DR. RAPPLEY: Is the committee agreeable to what Dianne has just described and ready to move on? Okay. Thank you.

So now we would like to proceed with

Dr. Sachs.

Celebrex (celecoxib)

Standard Review of Adverse Events

DR. SACHS: Okay. Thank you very much.

We're going to continue discussing some risk-benefit and Celebrex. Dr. Siegel set up some of the information that was presented at the advisory committee and I just do want to emphasize there was actually a lot of discussion of risk-benefit then, but what I'm going to do, if I can figure out how to move these slides forward, -- it's locked, Carlos. There we go.

Is present some of the details of the clinical trial and the adverse events and then pretty much conclude with the plans for further study which is what was decided at the advisory committee.

Now Celebrex is marketed by Searle and it's non-steroidal anti-inflammatory that was originally approved in December of 1998. Pediatric exclusivity was granted in August of

2006 and the pediatric JRA indication was awarded in December of that year.

In adults, celecoxib is indicated for the treatment of various types of arthritis, acute pain, dysmenorrhea, and as adjunctive treatment to reduce the number of adenomatous polyps in patients with familial adenomatous polyposis or FAP. JRA is the only pediatric indication.

The dosage depends on the indication with dosing ranging from a 100 milligrams to 400 milligrams twice daily in adults and in JRA, the doses are dependent on weight. Patients between 10 and 25 kilos are to receive 50 milligrams twice a day and patients that weigh over 25 kilos can receive a 100 milligrams twice a day.

Now to put the drug use in perspective, celecoxib was used -- the use of celecoxib was compared to lefluonomide which is a pyrimidine synthesis inhibitor, an immune modulator, as well as the large variety of non-steroidals you see here on the slide.

Not surprisingly, celecoxib is

primarily used in the outpatient setting with the majority of the sales by retail channels and the bulk of use is in adults and when compared to the other agents, celecoxib use ranks about third in terms of prescription volume.

Overall in adults, there was a slight trend to decrease use since the drug was approved in the period that we're discussing, although there was a slight trend, about a 2 percent increase, in the postexclusivity time.

Now in pediatric patients, the use represents less than 1 percent and celecoxib is much less commonly used, about eighth in the rank of all these agents, but the trends in prescription volume are very similar to that in adults. It's about a 28 percent decrease from the baseline period and a modest bump once exclusivity was granted.

This is just a graphic depiction of that bump. This slide does exclude ibuprofen and naproxen because otherwise we'd have to make things too tiny for us older eyes to see.

Now a significant amount of use is actually off-label, particularly for sprains and strains, and less than about 4 percent of use is related to the approved indication in children and duration of use has appeared to shift somewhat with at first in the baseline period, there was this kind of bimodal use, very short term, 8 to 15 days, and very chronic, greater than 91 days, but you can see during the postexclusivity period, about 67 percent of use is really in a 16-to-30-day frame.

All right. Now let's look at the pediatric exclusivity studies and the labeling changes.

There were several studies performed. The ones I'm going to focus on are two relative bioavailability studies which looked at the capsule and suspension which is what was used in the trial in adults and then relative bioavailability of the intact capsule and the capsule sprinkled over applesauce also in adults, and as you have heard, there is a clinical

efficacy study that was done, the non-inferiority study with the two doses of celecoxib versus naproxen.

Note the bioavailability appears to be slightly different between the capsule and the suspension which is what's marketed and that did impact that dose selection you see in the labeling.

Some other factors that impacted the dose selection is that clearance was lower in adults -- I mean in young children compared to adults, although the clearance in adolescence is very similar, and this difference really does seem to be related to weight.

In addition, dose selection was impacted by the following considerations. During the trial, the exposure response analysis suggested that a higher dose was needed to achieve an early response. We wanted to obviously identify a dose that was within the efficacy margin and did not exceed the safety margin that was identified by the trial as well.

Consequently, the pharmacokinetic findings are described in the PK Section of the labeling under Special Populations and the labeling has been changed to reflect the dose selected.

Now the efficacy trial findings were presented in detail at the advisory committee, as Jeff alluded to, but just in case you weren't there, the efficacy trial was an active control trial comparing two doses of celecoxib with naproxen and that established non-inferiority of both doses used and notably there was significant improvements in all measures of the JRA DOI-30 which is a clinical scale that uses laboratory as well as patient and physician reports related to the degree of arthritis, limitations of motion, and the joint involvement.

The findings are described in the Clinical Section of the labeling, including that long-term safety, particularly cardiovascular toxicity, has not been evaluated and the new indication for JRA has been added to the

Indications and Uses Section and the information is reiterated in the Precautions, Pediatric Use Section, and as well there's a description of the risk of abnormal coagulation tests in patients with systemic onset JRA, a finding that was not actually in the trials but came out of other information in the literature and practice.

Now Dr. Siegel has also described the safety findings of the trial in detail, but I just want to emphasize there were no deaths in either the 12-week placebo-controlled portion or the open-label extension, and the most common adverse events included gastrointestinal infections or infestations and CNS system disorders. Serious adverse events were noted a little more frequently in the low-dose arm compared to naproxen but there wasn't a clear dose response seen, and the observed adverse events did not actually differ from what we expect from other non-steroidals.

So, the labeling does reflect this. The most common adverse events are listed as you see and include some symptoms that I would say are

related to infections, such as headache, fever, abdominal pain, cough, nasopharyngitis, GI upset, diarrhea, vomiting, and arthralgia.

There was not a deleterious effect on growth observed nor was exacerbation of disease noted as evidenced by uveitis or flares in systemic JRA, and there's a table, of course, of the adverse events.

Now as you've heard, the postmarketing commitments are designed to explore further the effects, particularly on blood pressure and as a secondary effect GI bleeding, as well as some enhanced pharmacovigilance, and the sponsor will describe that, I think, a little more in detail.

And again, I just want to highlight some of the labeling that, you know, kind of explains some of the adverse events and relates to the adverse events that we saw.

As you know, all non-steroidals now carry a box warning regarding increased cardiovascular risk and GI bleeding, and for

celecoxib, in particular, there's contraindications related to allergic reactions to patients that have allergy to sulfonimides because of cross-reactivity, and as well as, in general, patients that are sensitized to aspirin or other non-steroidal products.

In addition to expansions of the contraindications and the box warnings, the warnings include some additional factors, such as hypertension and the need to monitor blood pressure, the risk of congestive heart failure and edema, the kidney effects, serious skin reactions, et. cetera, and I guess of interest to me as a pediatrician and you all and to avoid in late pregnancy because of premature closure of the ductus and there is, of course, a bolded warning that treatment in FAP does not necessarily preclude the need for surgery.

Precautions also include a general admonition that celecoxib is not to be a substitute for steroids and if steroids are to be discontinued, they shouldn't be discontinued

abruptly but tapered, and that it should be avoided with other non-aspirin or non-steroidal products and that it may impair the ability to detect clinical signs of infection, such as fever, swelling.

Both hepatic and hematologic adverse events can be seen. There can be mild elevations of liver function in up to 15 percent of patients and significant elevations in 1 percent and although anemia is fairly common, changes in platelet counts are unusual, except occasionally in the patients with systemic JRA who appear to be at more risk for DIC.

Periodic monitoring, of course, is recommended.

I just want to mention for this part of the slide, that it is excreted in breast milk as there was one event in a breast-feeding baby.

The current labeling reflects numerous reviews by the Office of Safety that you can see as part of our postmarketing activities and here are the raw counts of the adverse events

which prompted those reviews you just saw and since market approval, there's been thousands, 28,000 reports in patients of all ages of which most have been serious, 18,000, and several have been related to deaths, about 22,380.

But adverse events in pediatrics, if we focus on them, roughly do parallel the use with 94 raw counts, that's less than 0.3 percent of the total, most of these are again serious, and 13 are related to fatalities, although as you'll see, most of them are related to duplicates or inappropriately attributed to children.

So, just to walk through those 13 fatalities, since approval before the exclusivity period, there were actually eight events but when we did a hands-on review of those, there's only three pediatric fatal cases.

During the one-year postexclusivity, there's five reports, but when you do a hands-on review, there's really only two, and again we excluded events that were duplicated, that really occurred in adults or events that were clearly

unrelated to celecoxib.

In the time prior to granting exclusivity, there were three fatal events and you can see the details of them on this slide and as you may notice, the first of the two are very highly confounded by the underlying cancers that children had as well as multiple medications and their underlying illness which may very well have been related to their cancer.

The last fatal report is a report of an adolescent male who completed suicide shortly after starting celecoxib, and as you know, cardiovascular risks are well known as is the risk of fatal hemorrhage, but suicide and depression are listed under adverse events.

That brings us to the one-year postexclusivity period. I did kind of skip over that preperiod. As Dr. Siegel mentioned, the adverse events were reviewed in detail for that advisory committee and has actually been publicly discussed.

As you can see from these raw events,

most events are in adults and pediatric patients represented only a small percent of the 6,000 or more adverse events. There were 19 serious adverse events attributed to children and five of these, which there's only two that were unduplicated, are related to the fatalities.

This is just kind of an overview of the cases. There were 10 unduplicated cases since exclusivity was granted. Two of them were fatalities. They occurred during a pilot study in patients with Ewing's sarcoma that were receiving celecoxib as part of chemotherapy regimens, and I'll discuss them in detail in a moment.

The eight non-fatal cases involved two reports of dyspnea, palpitations, and pulmonary embolism as well as single reports of bolus eruptions, that was the one with the breast-feeding baby, intracranial hemorrhage, GI bleed, chest pain and blood clots, and most of these events, although labeled, really were actually highly confounded by either the patient's underlying illness, multiple medications, and

several of the patients had cancer as well. So, their association with celecoxib in particular is really unclear.

Details of the two fatalities are provided on this slide and this kind of description is somewhat what we saw in the other events. Both of the patients were receiving celecoxib, as I mentioned, as part of a protocol for Ewing's sarcoma.

The first died after progressive sepsis, GI bleeding, and multiple organ failure and the second died after radiation pneumonitis, pancytopenia and pericardial effusion associated with cardiac arrest, and these events seemed to be confounded by the underlying carcinoma, chemotherapy or radiation therapy, but do highlight, as did the event, the fatal events before exclusivity, of the off-label use of celecoxib that occurs, too.

So, in summary, the labeling has been updated with the new pediatric indication, the JRA indication, the dose and limitations of the study,

and the long-term complications are reflected in the labeling. The adverse events incorporated do include a risk of DIC in patients with systemic onset JRA, and the common adverse events.

There really were no new unexpected pediatric adverse events identified during our one-year postexclusivity review, but the data from the studies that are going to be happening focusing on safety assessments are still pending and, you know, we really think that's what should be looked at.

The plan for the studies is going to be presented by the sponsor and a follow-up report will hopefully be presented to you all once these postmarketing commitments come in, if you guys concur with the plan.

And before I call up the sponsor, again I just want to acknowledge the contributions of quite a few folks to this review.

Clarification Questions

DR. RAPPLEY: Can you clarify for us the plan that you would like us to concur with?

DR. SACHS: I guess that the clarification is that you're okay to wait till we present the PMCs and I guess that we just return to routine monitoring which does not mean no monitoring.

As you can see, there's quite a bit of monitoring that goes on, even in the routine situation, to generate all those reviews.

DR. RAPPLEY: So, the label changes that you described have already been made?

DR. SACHS: This is correct.

DR. RAPPLEY: And what you are asking us then is to agree with your plan to gather more information in the postmarketing commitment?

DR. SACHS: Correct. Because we think that's where we're going to see.

DR. RAPPLEY: And then we consider whether or not further changes need to be made?

DR. SACHS: Right.

DR. RAPPLEY: Okay. Are there questions for Dr. Sachs? Perhaps at this point we could take clarifying questions and move to the

sponsor presentation and then move into discussion.

Dr. Notterman?

DR. NOTTERMAN: Can you please restate the proportion of use that's off-label for this drug in the pediatric population?

DR. SACHS: Sure. I'll go back to that slide. And again this was in the children. Sorry that I'm not moving so fast and numbers are not my forte, so I'm going to look at the slide.

Thirty-three percent was in sprains and strains and 16 percent was in osteochondropathy which is fairly non-specific, and only 4 percent was related to the JRA indication.

DR. NOTTERMAN: Thank you.

DR. RAPPLEY: Other questions?

(No response.)

DR. RAPPLEY: Okay. Thank you, Dr. Sachs.

DR. SACHS: Thank you, guys.

DR. RAPPLEY: Move to sponsor

presentation.

Pfizer Comments

DR. CAWKWELL: Well, hello. My name is Gail Cawkwell. I'm a pediatric rheumatologist and an employee of Pfizer. I'm also the Global Medical Team Leader for Celebrex and I'm joined here today by a number of colleagues to help answer questions as needed.

My focus today, as was discussed earlier, is really on the postapproval commitments, both things that have begun or have begun to obtain results and those that we finalized details on and are looking forward to beginning soon.

The first thing I'd like to note, though, very quickly, as we've already heard from both Dr. Sachs and Dr. Siegel, is that the basis of the approval of Celebrex for JRA was a 12-week pivotal randomized double-blind active-controlled study comparing two doses of celecoxib to one dose of naproxen suspension, naproxen being the most commonly-used NSAID for JRA.

This was followed by a 12-week open-label extension at the higher dose of celecoxib and this resulted in an approval, as we again saw earlier, for relief of signs and symptoms of juvenile rheumatoid arthritis in children ages 2 and older.

The dosing is as indicated and as discussed earlier with two different dose range. For smaller children, 50 milligrams BID, and for larger children, 25 kilos and above, at a 100 milligrams BID.

Notably, the capsules open easily for children who can't swallow, can be put on a teaspoon of applesauce. It's flavorless, and the 50 milligram capsule was not previously marketed but very quickly after approval, that 50 milligram capsule became commercially available and is currently marketed in the United States.

In addition to routine pharmacovigilance, we entered into four postapproval commitments that I'll go over in a bit of detail. The independent pediatric expert

panel, an active surveillance program, a prospective observational registry, and a clinical blood pressure and safety program.

Let's start with the expert panel as this is rather an umbrella over all of our safety activities.

The objective of this panel is to really review pediatric safety data on Celebrex, regardless of the source, with a focus of providing advice and guidance as relevant to patients with JRA. This consists of five pediatric experts, a general pediatrician, as well as four pediatric specialists, a pediatric rheumatologist, nephrologist, gastroenterologist, and a hematologist with specific thromboembolic expertise.

The panel's already met twice. This is consistent with our commitment. They met in June of last year and December of last year. At each of these reviews, they reviewed a number of serious and non-serious cases, at that point reported through pharmacovigilance, and came to

the conclusion that there was no change in the risk profile of Celebrex for children with JRA, a conclusion that I believe was reflected earlier by the FDA reviewers.

The next meeting of this group is scheduled for this June.

The active surveillance program is something that Pfizer is undertaking that's really in addition again to our routine pharmacovigilance. This involves approaching pediatric rheumatologists and querying for serious adverse events and the way this looks is we're partnering with an organization called the Childhood Arthritis Rheumatology Research Alliance or CARRA.

They're a non-profit consortium of North American pediatric rheumatologists, and they will be doing a survey every month querying for serious adverse events amongst pediatric rheumatologists, and this will be about all NSAIDs, clearly including Celebrex but all NSAIDs, in children with JRA.

Twice a year, they will be a bit more extensive to obtain some sort of denominator type of information about how many children the clinic sees with JRA or treats with JRA.

I can give a little update on the information on the bottom of the slide where I note that a 149 pediatric rheumatologists have been invited to participate and at 39 sites. We currently have a 105. We currently have about 61 sites have expressed interest in participating and certainly from our point of view at Pfizer, any sites in the U.S. that are interested in participating, we'd welcome.

IRB approvals are ongoing and we hope to have the first survey cycle going out very soon.

The prospective observational registry is a way also to gather a bit more long-term information. Clearly, the standard for approval for a drug for a chronic condition like JRA we met in terms of a 12-week study.

However, longer-term events or events

that may take longer to be noted may not be seen in a 12-week study, even with that 12-week extension. So, our proposed registry is designed to gather more experience and to monitor longer-term safety in children being treated through regular clinical practice.

This is a non-randomized and non-interventional registry. So, children who are being treated for JRA and their doctors already made a decision to put them on Celebrex or to put them on another NSAID will then be enrolled and will be followed prospectively.

The minimum duration of follow-up in the registry for all children is two years. We anticipate the registry will take two to three years to enroll the 200 children on Celebrex and the 200 children on other NSAIDs. So, adding in those two years of follow-up, some children will be followed as long as four to perhaps five years.

Clearly, we'll be collecting all adverse events, although the focus will be on serious adverse events, particularly those around

cardiovascular, gastrointestinal, and hypertension-related adverse events.

These adverse events will, of course, be reviewed by our expert panel, as you saw in the prior slide, on an ongoing basis and, of course, be submitted to regulatory authorities in the normal manner.

We submitted a protocol to the FDA about this registry in May of 2007, as we agreed to in our commitment, and at this point, we have got an agreement with the FDA on the protocol design and believe we should be ready to start the study first thing next year.

A blood pressure study represents another commitment and the final one I'll talk about. This is a prospective randomized double-blind active-controlled study to look at the effect of Celebrex and naproxen on systolic blood pressure.

It's well known that NSAIDs affect blood pressure in adults. This is clearly labeled for all NSAIDs, but the impact on children is less

clear and as Dr. Siegel said earlier, with the pediatric population having more risk factors for hypertension, understanding the effect of NSAIDs, particularly Celebrex, on blood pressure seems to be very important, and we certainly agree at Pfizer.

This study will enroll children between the ages of 2 and 18 years and they will be randomized to Celebrex at the approved doses or naproxen. They will be followed for a period of six weeks and the primary endpoint will be change in systolic blood pressure.

While the main focus will be cuff pressures, there also is some interest in looking at ambulatory blood pressure monitoring in the subset of patients.

Again, the initial protocol was submitted to the FDA, as per our initial agreement in April of 2007, and we've recently come to a preliminary agreement on the protocol, and at this point, we anticipate starting the study by midyear of 2009.

So, in conclusion, to support the JRA approval, we at Pfizer agreed to implement what we feel is a robust postapproval safety program.

Our pharmacoviligance to date, including our own assessment as well as the involvement of our independent expert panel, have really revealed no new safety concerns for children with JRA.

Two of our postapproval commitments, as I've just outlined, the independent expert panel and the active surveillance program, are underway and with the active surveillance program again that first cycle is about to go out.

The two postapproval commitments have really made very good progress and we look forward to starting those programs in 2009.

Thank you very much for your attention.

Clarification Questions and Question to the Committee

DR. RAPPLEY: Thank you. So, this is open for discussion now and the question is

whether or not the plan that is presented for postmarketing commitment as presented both by the sponsor and then to use information from this plan to consider label changes at some point in time in the future.

DR. MURPHY: I think maybe a little background. We could have just recommended return to routine monitoring and we've got a lot of studies ongoing, but we thought that the process here, you know, that committee deliberated all day on the risk-benefits and part of the approval process was that these postmarketing studies for safety basically be done and so we thought it rather presumptuous to assume that you wouldn't want to hear about them.

But you could tell us that you don't want to hear about them in 2000 and whatever and we don't have to come back to you. So that is an option, if you want to tell us that, but that's why the question is sort of awkwardly phrased, is that we don't have anything really that we see in the way of safety signal right now, but we also

know that we have a large number of commitments or significant number of commitments by Pfizer to provide some safety updates and we were assuming you would want to hear about it.

So that's why we put the question that way. If you don't, you can tell us so, please.

DR. RAPPLEY: Discussion? Yes, Dr. Notterman?

DR. NOTTERMAN: Dr. Murphy, is there any way that the agency and this group can capture some of the information embodied in the 96 percent of patients, children receiving this who are not on label and so are not encompassed in this comprehensive and excellent program.

DR. MURPHY: The only -- and I'll let Pfizer tell me if they have something -- I think it would be wise to go ahead and let Pfizer say first what they have to offer and then I'll tell you what else is available.

DR. CAWKWELL: Just to say that of the four programs, you're right, that some of the

programs specifically focus on the approved JRA indication.

The expert panel, however, is really focusing on data from all sources. For example, related to FAP, there is a postapproval commitment to study children 10 to 18 with familial adenomatous polyposis. Safety data will be generated from that as well on children.

As you saw, many of the safety reports relate to investigational uses with INDs that have been opened by NCI and others, and safety information we receive on that is reviewed by that expert panel, and we were careful to have some sort of a hematology oncology thromboembolic expertise to help us with those areas.

So, there is a broader scope of review there as well.

DR. RAPPLEY: Dr. Ward?

DR. WARD: Could I just ask? In the oncology uses of Celebrex, is the dose significantly higher than is used for the anti-inflammatory responses for JRA?

DR. CAWKWELL: Would you like me to answer that question?

DR. WARD: Yes.

DR. CAWKWELL: I think it depends on the indication. So, I've seen research protocols in children that run a range. I believe in one study I looked at recently, perhaps it was the Ewing's study, although I don't -- I'm not certain of that, it was a 50 milligram BID dose that was being used which was a relatively low dose.

For example, the FAP study, the pivotal study that led to the initial indication, was not in children but used a 400 milligram BID dose which is substantially higher.

So, I think that there's a wide range.

DR. SIEGEL: I just wanted to respond to the question about the 96 percent of children who don't have the approved indication.

Our particular concern in designing the postmarketing commitments for celecoxib were concerns about the safety of the long-term use. A

lot of the unapproved uses are short term, like for sprains, so it wouldn't have the same concerns about cardiovascular risk and so on.

DR. RAPPLEY: I'd like to ask --

DR. MURPHY: To finish up, I mean, other than that, it's the AERS passive reporting system and again to remind the committee, as you'll hear later, most of that is already -- the majority of that in the AERS system we get from the sponsors, but it is available to any practitioner to provide input into that system.

DR. RAPPLEY: Dr. Kocis?

DR. KOCIS: I was just going to follow up that, you know, again these follow-up studies, I thought, were extremely well designed and are comprehensive for patients with JRA who will see this drug for likely their lifetime.

I was a little bothered when you saw the short-term size. Clearly, the registry and the other things are long term and what needs to be followed in those patients since they will be for so long and yet when we talk about the 96

percent that are using it off label, while yes, it's only for short-term use and maybe that's a good thing, they are also going to be given to children who may be immobilized, who may have other risk factors, who may be on oral contraceptives or a whole host of other illnesses that may lead them to have a much higher risk in the short term, and yes, we have a current AERS method and that would certainly be what we would see and would be highly effective and yet I would think, given the national acclaim over this drug and all the concerns about that from many, many standpoints, that there would be a more active or yet another way to try to capture data sooner, earlier, better in that group of patients.

DR. RAPPLEY: I would echo that, being that it's eighth in volume for pediatric patients. So, if it's eighth in volume of number of prescriptions written and 96 percent of those fall into a category that won't be studied, it does give one pause.

DR. CAWKWELL: If I can maybe put

that into a little context for you, if we could put up Slide B-11, when we say that it's less commonly used or that it's second or third, here's some information from a very large pediatric rheumatology center in Cincinnati that kindly provided their data, and you can see that while Celebrex is not one or two nor number 10 on the list, its use is really low. It's been consistently lower over a number of years and so that sort of use, I think, remains rather low when compared to other NSAIDs.

DR. RAPPLEY: So, maybe I misread this then. Dr. Sachs, will you clarify your Slide Number 8 that says it's eighth in terms of prescription volume? Is that of all medications or is that only medications for JRA?

DR. SACHS: That's the selected group of non-steroidal agents during that, you know, --

DR. RAPPLEY: Thank you.

DR. SACHS: -- time frame.

DR. RAPPLEY: Thank you. And then I had a further question about Phase 4 studies. So,

how are the four elements or the four types of studies that have been presented to us as postmarketing commitment, how does that -- is that compatible with the agency's expectation for Phase 4 studies of this medication?

DR. MURPHY: Right. These are the studies that were agreed to at the time of approval for phase after it was approved for postmarketing, observations and data collection.

DR. SIEGEL: Could you repeat the question? I didn't understand what you were driving at with your question.

DR. RAPPLEY: For me?

DR. SIEGEL: Yes.

DR. RAPPLEY: About Phase 4? So, I understand from our previous discussions about this medication that there was a commitment at the point of approval to Phase 4 studies.

So, I just want to clarify whether or not the plan that's been presented by the sponsor is in keeping with what the agency and what the committee could fairly expect with Phase 4

studies.

DR. SIEGEL: So, the studies that Pfizer is undertaking as postmarketing commitments were the studies that the division asked for and that Pfizer agreed to do.

It's a little bit difficult to generalize the kinds of postmarketing things we would expect for a disease-modifying product, like a TNF blocker, and be quite different from the kind of postmarketing studies we might expect for a non-steroidal that's expected to give symptomatic relief, but these are the studies we thought were warranted for this particular product with its risk-benefit profile.

DR. RAPPLEY: Dr. Notterman?

DR. NOTTERMAN: I wonder, Dr. Siegel, if you have information concerning the kinds of practitioner, the specialty of practitioner, who's prescribing the 96 percent off-label use? Is it general pediatricians or orthopedists or pediatric rheumatologists?

DR. RAPPLEY: That's on Slide 8 of

Dr. Sachs' presentation. She -- at least that same population.

DR. SACHS: Well, actually, my recollection is the pediatric use is relatively so small that the majority of the practitioners were the adult practitioners and I don't think it got broken down to what type of pediatricians or what type of, you know, pediatric specialists were prescribing.

DR. RAPPLEY: So, when, on Slide 8 then, are we talking about, when we say general practices, 30 to 35 percent of prescriber specialty, --

DR. SACHS: Those are adult practitioners.

DR. RAPPLEY: Right. But are they prescribing for children?

DR. SACHS: They're prescribing celecoxib in general.

DR. RAPPLEY: Okay.

DR. NOTTERMAN: Just to clarify, so for the children who are receiving this drug, do

we know who's prescribing it? No.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Just a question about the independent pediatric expert panel. Does that mean that they're selected by and/or paid by someone other than Pfizer?

DR. CAWKWELL: No, it does not. They were both selected and they are being paid for by Pfizer. They are independent academic practitioners and it's certainly our intent that they behave and give us advice that will be useful with regards to labeling, to making recommendations back to the FDA if they see a signal, and I think our approach to them is to treat them as we might treat, say, a DSMB.

DR. SACHS: Marsha, can I clarify, also? If you guys look, there's the use by Laura Governale on Page 3. This is the total number of drug occurrences reported by office-based physicians and it says that approximately 66 percent of drug occurrences appeared to be from orthopedics who were prescribing to the kids.

DR. RAPPLEY: You said Page 120 in the binder?

DR. SACHS: 119.

DR. MURPHY: So, Page 119 then is where we're supposed to be looking?

DR. SACHS: Yes.

DR. MURPHY: Okay.

DR. RAPPLEY: So, I'd like to follow up on Dr. Newman's question. I've been sitting too close to him probably today.

Is it fair to call this an independent pediatric expert panel? Is that somewhat misleading to use that descriptor? He doesn't have to be the only person raising those kinds of issues today.

Dr. Garofalo?

DR. GAROFALO: Well, it's certainly an independent view from the safety. Of course, there'd be a large safety staff internally in Pfizer. So, it's a separate specialist outside of and I don't know, you know, how you charter them, et. cetera, but --

DR. CAWKWELL: I would note in terms of, for example, charter, that they do have a specific charter. They have specific rights that are outlined, for example, for the chair and the contract to, if they disagree with our stance, to come directly to FDA which I would hope, even without that in the contract, they would feel free to do.

So, I think you can argue about the choice of the word "independent." By independent, I mean that they're not employees of Pfizer and I hope if you were talking to them, that they would reflect that they feel that they're behaving in an independent manner which is our expectation of them.

DR. RAPPLEY: Dr. Sable?

DR. SABLE: Well, it would seem to me that the biggest concern, which would be in my mind one of the hardest things to answer, is are these children taking this medicine going to have the same long-term risks that adults are having in terms of cardiovascular events and are these

events going to be premature?

So, kind of a two-part question. Number 1. Are there plans to follow up these patients for decades to see if and when these risks occur, and also are there any type of studies that are looking at the vascular risk in these children, things like cholesterol panels, brachial reactivity, carotid intimal thickness, things that actually can assess vascular risk profile even before it occurs?

DR. CAWKWELL: I can address in part, if that would be helpful.

Pfizer is also undertaking the Precision study. It's a postapproval commitment as well for looking at 20,000 adults with osteoarthritis and rheumatoid arthritis who either have cardiovascular disease or at risk of cardiovascular disease. They'll be followed for a minimum of 18 months, although many of the patients will probably be followed three or more years.

Now while those are adults, it may

reflect on if you're a child with JRA and you grow up to be an adult and you're now followed by an adult rheumatologist, this may help reflect a bit on outcomes.

The issues that were discussed quite extensively during the advisory committee meeting around the approval of this JRA indication was the very, very low frequency of cardiovascular events in children, including children with JRA.

The lack of knowledge on the etiology of cardiovascular events related to NSAIDs and the feeling was learning more about hypertension and that the Precision study, again looking at a very large cohort of adults, may help fill that gap.

DR. RAPPLEY: Dr. Siegel?

DR. SIEGEL: So, I think the question relates to how we can assess in children the potential risk of cardiovascular disease given what we know in adults, and this is something that we thought long and hard about in the agency, to try to design a study that would give us some information about this, but you run into some

difficulties when you try to design such a study.

The studies in adults suggest that the risk of cardiovascular disease is increased by 30 to 100 percent on that order, but since cardiovascular disease is so uncommon in children, how do you follow enough children for long enough to see what the risk might be, because the risk for cardiovascular disease might not appear until decades later, and then you run into the problem that people don't start on one NSAID and continue on the same NSAID continuously for decades. They take it for awhile and then stop and try another one.

So, even if you did have a large number of children followed even for decades, what to ascribe an event that happened decades afterwards to would be very difficult.

What we tried to do is to design a study with Pfizer that would collect some helpful information on long-term use, understanding the limitations. If you all have other suggestions about other things that might be studied, we'd

certainly be happy to hear.

DR. SABLE: So, what I'm hearing is there's really no studies looking at the acute, the kind of short-term assessment of vascular reactivity, although there is plenty of literature in other disease processes to do some of the events that -- do some of the testing that I talked about in terms of vascular reactivity or carotid intimal thickness.

DR. CAWKWELL: I would also note for vascular reactivity that short-term studies in adults suggest that Celebrex improves vascular reactivity in adults with coronary artery disease and yet how predictive that is of long-term cardiovascular safety in adults, I'm not sure in this particular setting. It's still a surrogate or an intermediate endpoint for some things with some uncertainty attached.

DR. RAPPLEY: Dr. Sandborg?

DR. SANDBORG: So, this is a very difficult area in rheumatology in general and in pediatric rheumatology because the incidence of

cardiovascular disease in these patients is so small and it really may take decades before we would see anything and whether we could even detect a signal at that point is important.

I guess there's a couple of points I want to make, that really all NSAIDs, except probably naproxen, increase the risk of cardiovascular, so ibuprofen does, and although we don't know the relative amounts, it is -- they all do to some extent.

I think also the issue of, you know, whether you can really do predictive studies, like IMT or brachial artery reactivity, is still out. In pediatrics, at least IMT is just beginning to be understood and we have an ongoing large study looking in lupus, which is a very high-risk type of premature atherosclerosis, and so we don't know if we're going to be able to detect it there with a very large signal of lupus compared to the very small signal of a non-steroidal, whether that would cause problems or not.

DR. RAPPLEY: So, the question is,

are we recommending that the agency proceed with their plan to support this as the postmarketing commitment and then come back to us at some point in time in the future with the results of this? Does the committee accept that recommendation?

Any opposed? Okay. Thank you. So, am I correct that concludes our discussion of medications and agents? I forgot Trileptal. Save the best for last. Dr. Mentari?

DR. MURPHY: I just want to repeat what I said this morning as -- for everybody is that just remind, because some of the committee wasn't here and some was, that in '06, in November of '06, we presented Trileptal to this committee and at that time, the Neurology Division provided to you an overview of what their plans were for looking at the potential signal for suicidality in the anti-epileptic product.

This committee at that time asked to be informed and be provided feedback on what the analysis showed and you specifically asked for a focus on pediatrics.

There will be a meeting, I don't think it's -- besides what it said in the announcement, it's still not public date yet, is that correct?

DR. MENTARI: That's correct.

DR. MURPHY: Okay. There will be a meeting this year, we think, on this topic. There is the public health announcement which was provided to you and at that time, at that meeting, members of this committee will be asked to join the Neurology Division Advisory Committee and the Risk Committee that will be augmenting the Neurology Committee, in addition to Pediatric Committee.

Is there another committee I've forgotten that's also been -- Psychiatry. Thank you.

So, this goal today is to make sure that you guys are informed of what's going on and we're open to questions, but it's really -- we're not posing a question to you. We just wanted to make sure that you were informed because you did

think about it and requested follow-up.

Thank you.

DR. RAPPLEY: So, this is for our information at our request and a full review will occur in the Fall?

DR. MURPHY: Or some time this year, yes.

DR. RAPPLEY: Okay. Thank you.

Updates on Previous PAC Request

Trileptal (oxcarbazepine)

DR. MENTARI: Good afternoon, and thank you for this opportunity to discuss our analysis today.

The Division of Neurology Products has evaluated the potential association between anti-epileptic drugs and suicidal thinking and behavior in placebo-controlled trials.

Postmarketing cases of suicidal thinking and behavior are difficult to interpret as there are no limitations of postmarketing data and patients with epilepsy and other illnesses for which anti-epileptic drugs are prescribed have

increased risks of suicide.

An anti-epileptic drug sponsor approached the division with concern of a suicidality signal in their controlled clinical trial database. In response, the division initiated an analysis of suicidality events in controlled clinical trial databases of all anti-epileptic drugs.

Sponsors were asked in March 2005 to provide data from their placebo-controlled trial experience. We performed a standardized approach based on previous FDA analyses of suicidality in children, adolescents, and adults treated with antidepressants.

In these analyses, pediatric and young adult patients treated with antidepressants were found to have an increased risk of suicidality compared with those treated with placebo.

In order to find possible adverse events of interest, we used the following search strategy. We looked at events with preferred

terms with texturing, suicide or overdose, including all events coded as accidental overdose, verbatim terms with texturings, intent, cut, gas, hang, hung, jump, mutilate, overdose, self-damage, self-harm, self-inflict, self-injure, shoot, slash, suicide, poison, asphyxiation, suffocation, and firearm. Events were screened for false positives.

All deaths and other serious adverse events were evaluated and all adverse events coded as accidental injury were evaluated.

Our analysis included parallel arm placebo-controlled trials with at least 20 subjects in each treatment arm. We excluded subjects under age 5 and the search was performed by sponsors using search terms specified by FDA.

After events were found using the search strategy, structured narratives were prepared and based on these narratives, events were classified into seven categories. Classification was done by raters who were blinded to treatment.

We asked sponsors to use the Columbia Classification Algorithm for suicide assessment which involved the following suicidality event classifications: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior, intent unknown, not enough information fatal and not enough information non-fatal.

Next, I will go over our overall results. This slide lists the anti-epileptic drugs which we analyzed. They include carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.

We analyzed data from a 199 placebo-controlled trials which include 43,892 patients, 27,863 of which were drug-treated patients and 16,029 of which were placebo-treated patients.

We found that drug-treated patients had approximately twice the risk of suicidal behavior or ideation compared with placebo-treated

subjects. We found a risk difference of 2.1 additional events in drug-treated patients per 1,000 patients with a 95 percent confidence interval of 0.7 to 4.2.

The increased risk was observed throughout the time periods for which data was obtained. We looked at trials that were at least one week in duration. Beyond 24 weeks in duration, we had very little trial information and beyond that period of time, we were unable to reliably assess risk.

There was no clear pattern of risk across age groups and the results were generally consistent across all drugs.

In this table, we have the event counts for the drug and placebo groups. Our primary outcome encompassed all four event categories that you see in this table. When evaluating these numbers of events, it's important to note that there are more subjects in the drug-treated group as compared to the placebo-treated group.

Next, I'll discuss our results by trial indication. Our analysis included 62 trials indicated for epilepsy, 56 trials indicated for psychiatric indications, and 81 trials with other indications.

The psychiatric trial indications included bipolar disorder, anxiety, posttraumatic stress disorder, depression, panic disorder, schizophrenia, social phobia, and binge eating disorder.

Other trial indications included agitation, chronic pain, impaired cognition, neuropathy, insomnia, migraines, spasticity, obesity, fibromyalgia, and tremor.

All of the drugs in this analysis are indicated for treatment of epilepsy. This slide lists approved non-epilepsy treatment indications.

In this table, we have the relative risk and risk difference according to trial indication. In the epilepsy trials, we saw the largest relative risk which was 3.6. In psychiatric trials, the relative risk was 1.6, and

in the other indications, the relative risk overall was 2.3.

In contrast, the risk difference was comparable between epilepsy and psychiatric trials. The risk difference in epilepsy was 2.5 per 1,000 patients; in psychiatric trials, the risk difference was 3.1 per 1,000 patients; and in other trials, the risk difference was 1.1 per 1,000 patients.

It's important to note that the rate of events in placebo patients per 1,000 was higher in the psychiatric trials as compared to the epilepsy trials and trials for other indications.

Next, I'll go over our results by subject age group. All of the anti-epileptic drugs, except for carbamazepine, had pediatric subject data. Because we excluded subjects under age 5, we defined our pediatric subgroup as subjects between 5 to 17 years of age.

We had data from 65 placebo-controlled trials and there were 2,411 total pediatric patients. 1,292 of those patients were

drug-treated and 1,119 patients were placebo-treated.

This table lists the pediatric events by treatment arm and placebo-controlled trials. There were no events of completed suicide. There were two events of suicide attempt in drug-treated subjects and no events of suicide attempt in placebo-treated subjects. There were no events of preparatory acts and there were three events of suicidal ideation in drug-treated subjects and one event of suicidal ideation in placebo-treated subjects.

It is important to note that the events in this table include only the most critical event for each patient and do not reflect multiple events in individual patients.

The trial indications in the pediatric data are different from that of the overall data. The vast majority of subjects came from epilepsy trials, 83 percent, 7 percent of subjects came from bipolar disorder trials, and 9 percent of subjects came from migraine trials.

This slide summarizes our odds ratio estimates of suicidal behavior or ideation by age group. The division's overall assessment was that there was no general pattern of risk across age groups.

In the pediatric age group, ages 5 to 17, the odds ratio was 4.26 with a wide 95 percent confidence interval of 0.58 to a 102.1. There are five suicidality events in 1,292 subjects who were drug-treated and one suicidality event in 1,119 placebo-treated subjects.

In the 18-to-24 age group, the odds ratio was 2.65 with a 95 percent confidence interval of 0.9 to 9.45, in the 25-to-30 age group, the odds ratio was 0.82 with a confidence interval of 0.31 to 2.27, in the age group 31-to-64, the odds ratio was 2.02 with a confidence interval of 1.26 to 3.36, and in the 65 and over age group, the odds ratio was calculated as infinite because there were three events of suicidality in 3,653 drug-treated subjects while there were no events of suicidality in the 2,056

placebo-treated subjects.

Overall, the odds ratio was 1.95 with a confidence interval of 1.33 to 2.92.

Given these results, we have issued a press release and information for health care professionals regarding the increase of risk of suicidal behavior or ideation with anti-epileptic drugs.

Class labeling for anti-epileptic drugs is in progress, and a joint advisory committee meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee is planned.

Drug Safety and Risk Management Advisory Committee members and Pediatric Advisory Committee members will also participate.

At this time, I'd like to acknowledge the work of the Division of Biometrics 6 which performed the statistical analyses and the input of DPP, OSE and DNP in this analysis.

Thank you very much.

DR. RAPPLEY: Thank you. Any questions? Yes, Dr. Ward?

DR. WARD: Could you clarify the difference between Slide 12, where the confidence intervals are .7 to 4.2, and your Slide 25? It's titled the same, that is Suicidal Behavior or Ideation, yet the confidence intervals are different. One's significant, one is not.

DR. NEWMAN: I think one's a risk difference and one's an odds ratio.

DR. MENTARI: Slide 12 and Slide 25, you were saying?

DR. WARD: So, am I reading it wrong?

DR. NEWMAN: I think one's a risk difference and then so it's significant in that it excludes zero, right, because it's a difference --

DR. MENTARI: That's fair.

DR. NEWMAN: -- and the other is an odds ratio, so it's significant if it excludes one.

DR. MENTARI: Right. They're -- as was mentioned, they're just two different

descriptors of risk.

Slide 12 has the risk difference, namely the fact that there were in all age groups 2.1 additional events of suicidal behavior or ideation in drug-treated subjects as compared to placebo-treated subjects, and in Slide 25, what we have there is an odds ratio, which is adjusted for several factors and so basically that's similar to a relative risk but it's a different -- so, there's approximately 1.95 times the risk of suicidal behavior/ideation in drug-treated subjects according to that statistic.

DR. RAPPLEY: Other comments or questions? So, we'll await, then, the results of the next full review.

DR. MURPHY: Yes, they're still -- as you know, we now try to get the information out to the public even before we're finished with all the analysis. They've really completed most of the analyses but are preparing for the meeting and weren't quite ready and, as I said, plan to invite members of the Pediatric Advisory Committee, but

we didn't want to have this meeting with you all knowing they were going to have another meeting without making sure that you were aware of what was going on.

DR. RAPPLEY: Thank you. We do have two more questions. Dr. Farrar and then Dr. Cnaan.

DR. FARRAR: Is there any way to look at older anticonvulsants, like phenobarbital and things like that, because these are all obviously new ones that have come out. I mean, you're looking at the clinical trials, but is there any way to get back to -- is this something that happens with all anticonvulsants or is it something that happens with the newer anticonvulsants?

DR. MURPHY: Well, I'd have to ask if we have randomized controlled trials of phenobarb.

DR. WARD: I can tell you that this is a debate in neonatology about phenobarbital and the people at Pittsburgh and people at CHOP both maintain there are no placebo-controlled trials to

look at.

DR. RAPPLEY: Dr. Cnaan?

DR. CNAAN: I would second that. The problem with the older drugs is that the nice thing about this analysis is that you're comparing apples to apples. Unfortunately, with the older drugs, we don't have the placebo group appropriately, so we can't just throw in the cases of the old drug because it won't be comparable.

So, I think that the analysis that has been performed is the best that we could hope for and then comes that extrapolation argument again. Can we extrapolate to the older drugs or not which is a discussion, but I think that we really cannot throw them into the analysis, and it was done correctly.

DR. RAPPLEY: Dr. Garofalo?

DR. GAROFALO: Yes, I'll just reiterate that having worked for a company that made Dilantin, I went back and looked. I mean, there just were no controlled trials.

So, even if you had controlled

trials, we don't know how the safety data would have been collected and what, you know, sort of mapping terms and all that sort of thing. So, I think it does have to be this group that was done with certain coding, et cetera, because it's on the safety side.

DR. HUGHES: Hi. This is Alice Hughes. I'm from the Division of Neurology Safety Team.

I just wanted to echo what you all suspected. The reason we didn't include the older drugs in our analysis was because they just didn't have clinical trials that met our criteria. So that's why they're not there.

We have no reason to believe that they would not share the same risk, I'll say, and the class labeling that we're working on is class labeling, not limited to the drugs included in -- the 11 drugs included in the analysis.

DR. RAPPLEY: Dr. Cnaan?

DR. CNAAN: My single question was the odds ratio on that almost-last slide, you

mentioned it was corrected for several factors. What was it corrected for or adjusted for?

DR. MENTARI: Give me a minute. I can look that up. Thank you.

DR. RAPPLEY: While she's looking that up, I have a question I'd like to ask about process and not about any particular product that we've talked about today, but, as we become more involved with the Best Pharmaceuticals Act and begin to carry out some mandates from that group, is there a process by which a sponsor commits to a certain timeline for the postmarketing commitment, and then are there people who are within the agency who are designated to track that?

DR. MURPHY: Yes and yes, and you can actually go on the Web now and see whether they're meeting their commitments.

Does anybody know the website name? But I think you can get to it from just going to the FDA page and -- no, the Phase 4 tracking. Yes, the Phase 4 tracking. I know that it's required now that it be public and where we are on

it and there is a way to get to it on the Web.

Do you have anything else?

DR. MATHIS: You can actually go by searching postmarketing commitments, you can pull up the website, and then you can search even further on that web page for Pediatric Research Equity Act postmarketing commitments.

DR. MURPHY: But you can do it for any product, too.

DR. MATHIS: Correct.

DR. MURPHY: Yes, you can just do it for any product, also.

DR. RAPPLEY: Would you like to respond to the question or do you need a little bit more time?

Any other questions or comments while she's looking at her information?

DR. MURPHY: I just want to say that, you know, this is an example of using information we learned. Many of you were here for the SSRIs, which that information came out of a meta analysis of the pediatric-controlled trials.

Yes, at the end, we added some other trials that weren't done because of the exclusivity activities, but almost all of those trials were pediatric trials done in response of exclusivity and we learned from that something about search terms and how better to look for this and so what you're seeing today is, again, being applied throughout -- besides pediatrics, some of the lessons have come out of pediatric studies. Nothing like a little advertising.

DR. MENTARI: Okay. So, the method of analysis was a stratified odds ratio and the stratification factor was a trial and basically the evaluation according to subgroup was achieved by stratification according to subgroup and not adjustment in terms of regression.

DR. RAPPLEY: Dr. Kocis?

DR. KOCIS: Just to comment when we meet next time, for all these age brackets, we've gone fairly broad from 5 to 17, and I was just hoping that when we come back next time, that we can see a better breakdown as to when this is

occurring.

Obviously, you would think adolescence and yet I'd be curious as to whether it's occurring earlier and likewise I think your denominator would change when we begin to exclude, possibly, the 5-year-olds who may or may not, I presume, were having less suicidal ideation and active commitments.

So, it would give me a better understanding of when and where and a better ratio.

DR. MENTARI: I guess one comment I have on that comment is that, you know, we're limited by the fact that our events are so sparse. Our total number of events in the age 5 to 17 age bracket was five events in the drug group and one event in placebo group and that unfortunately limits us in our ability to further delineate how that works within that age group.

DR. RAPPLEY: Dr. Cnaan?

DR. CNAAN: Page 350 at least gives you the denominator. There is an age distribution

on Page 350.

DR. RAPPLEY: Okay. Thank you very much, and are we ready to --

DR. MURPHY: I wanted to thank the division very much, too, because they really did a superb job of making sure that they had this information available for you all before they were really ready, if you will, to go public. So, I personally want to thank the division for getting this done for you all.

DR. RAPPLEY: Okay. So, now we move into the portion of the meeting where it's more educational, kind of preparing us for our future mandate or the mandate which we currently have and will be acting on as of our next meeting.

I know that some of you have to leave early, so please don't apologize for that and just leave as you need to.

Just in opening this, I guess I would like to comment that I was struck by what Dianne has written to us, that in fact of 11 titles written into the new legislation, our committee is

named in three of those titles as specifically responsible for considering the issues that are so unique to children and I believe that Congress is responding to the advocacy of groups like the American Academy of Pediatrics and some of our scientific associations and discipline-based societies that have consistently said that children are not small adults, that we need to consider their safety and take a more protective role and a more proactive role in this and Congress has responded to that.

Now they gave us the job in part and so it increases our responsibility but really it's a great privilege, I think, to be given the task now and to see that kind of responsiveness on the part of our legislatures and our government and it really is in response, I think, to the hard work that was done by so many pediatricians and others across the country.

Dianne?

FDAAA 2007 - Pediatric Perspective Update

Brief Overview of Legislation

DR. MURPHY: Thank you. I did want before people start phasing out, for those of you who are not rotating off the committee, we are going to have a training session this Fall and we have a lot.

This session now is just to give you an idea of what you're in for and why you need to come to training and particularly the new people because we're going to go over labeling and, you know, what authority the agency does have, what it doesn't have, direct consumer advertising, all that sort of stuff, give you an idea of the context in which all of this is happening.

So again, we're asking a lot of you, we understand we're asking a lot of you, but we really do hope you can make your training, and Carlos is going to be getting dates from you, right, Carlos, for that.

So, this today is what's happened with FDAAA and why it affects you, and I am very quickly going to go through for the new members in particular the series of legislation.

This actually started -- just think of sevens. This all starts back in 1977 when the American Academy of Pediatrics said we have to stop doing this. We have to stop treating children without data and we have to start getting controlled trials and it took a long time before we actually got some legislation which the first incentive program was in 1997, the first rule was in '98. We lost in the law and the courts and they enjoined us from enforcing it in 2002.

We had then a sunsetting of the exclusivity or incentive. We had the Best Pharmaceuticals Act which then came to replace that and we had the Pediatric Research Equity Act which then was passed to say yes, FDA does have the authority to require studies in certain situations.

So, those were our two work horses or the three FDAMA, BPCA and PREA have been the work horses that have really generated over 300 written requests from the agencies for studies for over -- I think we're up to, what, Skip, is it 800