from all four pediatric studies. The results and conclusions were that interpatient variability of oxaliplatin clearance was 41 percent and pharmacokinetic parameters in pediatric patients were similar to those seen in adults.

The activity endpoint was the objective response, that is complete response plus partial response, in patients treated for two to 17 courses per year. Within the four pediatric exclusivity studies, only one partial response was observed, resulting in a response rate of 0.25 percent. Thus, the medical reviewer concluded that oxaliplatin is ineffective in the regimens that were tested in children with refractory solid tumors.

For the safety analysis, there were a 109 pediatric patient deaths across all four studies, the vast majority of which occurred greater than 28 days after the last oxaliplatin dose.

Twenty percent of the patients in the Phase 2 studies had non-fatal serious adverse

events and 8 percent of patients across all four studies withdrew their study participation due to an adverse event.

In the end, the medical reviewer concluded that (1) the adverse event assessment was difficult in such an end-stage population, (2) all deaths were clearly or likely due to disease progression and expected in a population with very advanced and refractory metastatic solid tumors, and (3) oxaliplatin safety profile in the pediatric population is similar to that in adults.

With regards to the 109 deaths, all deaths in the Phase 1 studies and in Study ARD5530 were due to disease progression. Twenty-one or 78 percent of the deaths in Study ARD5021 were due to disease progression with the remaining six deaths being classified as unknown or other causes.

You will note that two of these six deaths were really in reality thought to be related to disease progression and the cause of death was unknown for the other four.

Moving to non-fatal serious adverse

events, such events were reported in 18 or 20 percent of the patients in the Phase 2 studies which you will recall utilized an oxaliplatin dose of a 130 milligrams per meter squared every three weeks.

The most common events reported were headache with four patient reports, hypersensitivity with three patient reports, and convulsions, infection and peripheral sensory neuropathy with two patient reports each.

The next slide describes the most frequently reported non-fatal serious adverse events seen in the Phase 1 studies which you will recall utilized a range of oxaliplatin doses.

As in the Phase 2 studies, sensory neuropathy was commonly seen in the Phase 1 studies, in addition to a variety of other events that are listed on this slide.

With regard to patient withdrawals, 13 or 8 percent of patients across all four studies withdrew due to an adverse event. The most common events leading to patient withdrawal

U.S. case, and then there was one death report that was from the United States.

Since there were so few pediatric reports during the postexclusivity period, the safety reviewer also assessed the pediatric adverse events since marketing approval. For pediatric patients, there were 15 adverse event reports which comprised 0.3 percent of the total reports. Of these 15 reports, eight were U.S. cases. All of the reports were for serious adverse events and again there were eight U.S. cases.

There were two death reports and both of these were U.S. cases.

Looking at the 15 crude count pediatric adverse event cases identified since marketing approval, seven of these cases were excluded due to being duplicate or miscoded cases. Of note, the two raw count pediatric death cases were actually miscoded cases that involved patients greater than or equal to 17 years of age.

The eight remaining cases were all

Surveillance and Epidemiology, the Division of Drug Oncology Products, and the Office of Clinical Pharmacology.

Thank you.

Clarification Questions and Question to the Committee

DR. RAPPLEY: Thank you. This is open for discussion. Dr. Cnaan?

DR. CNAAN: I think this demonstrates the issue that we've raised before. It's not the question before the committee but the language is effectiveness of oxaliplatin in children has not been established.

I think here, it's established that there isn't effectiveness, given that it was well designed to get to the MTD and then we had no responses basically. So, it's not before us. We don't need to deal with this, but there is a difference between effectiveness not being established and it is established as non-effective.

DR. RAPPLEY: Other thoughts about

that? Dr. Newman?

DR. NEWMAN: I would echo that, but first I want to just say that the thought that comes after that, the five paragraphs describing the studies, I think, is just right and just what was intended in the BPCAs. I'm really happy that that -- it's different from the last case.

Once again, there's no efficacy but here, there's the detail that allows a person to actually look at the label and see the value of the studies that were done. So, I think that's great and I would agree with Dr. Cnaan to just change the first sentence that oxaliplatin appears to be an effective and if you just say in that first sentence or that second sentence, 159 patients treated with only one partial response, that's really clear, much more clear than just no significant activity. One partial response out of a 159 patients kind of gives the message pretty clearly.

DR. MURPHY: I think that, you know, these are refractory patients. So, we want to

point that out.

I think that this is an example of where the division felt that it was really important to provide a significant amount of information and not just leave it at, you know, it doesn't work, but here's the dosing we tried, here's how we push it and this is how it didn't work.

So, I think if you read beyond the first sentence, you'll understand what they were trying to explain in refractory patients in that population. So, as we said, you're seeing products over time that had issues over time and addressed it over time in different ways, and also whatever the background disease is is going to require somewhat of a different approach, also, and I'm glad you all like this label.

DR. RAPPLEY: Other comments? So, does the committee then accept this recommendation that this medication be moved to routine monitoring?

(Show of hands.)

DR. RAPPLEY: Any opposed? Okay. So, unanimous vote to make that recommendation.

Thank you. So, we'll switch to the next medication now.

Colazal (balsalazide)

Standard Review of Adverse Events

DR. COLLINS: Okay. Now, I'm pleased to be able to present to you the one-year postexclusivity adverse event review for balsalazide.

Colazal or balsalazide is a 5-aminosalicylate for which Salix Pharmaceuticals is the drug sponsor. Original market approval occurred on July 18th, 2000, and pediatric exclusivity was granted on August 23rd, 2006.

Prior to the pediatric exclusivity study, balsalazide was indicated for the treatment of mildly to moderately active ulcerative colitis.

The next two slides provide information about the use of balsalazide in outpatient settings. Approximately 360,000 balsalazide retail and mail order prescriptions

were dispensed for all age groups during the 12-month postexclusivity period. 2.7 percent of these prescriptions were for the pediatric population.

There was a 4 percent increase in retail prescriptions for all age groups between the 12-month pre- and postexclusivity periods and a 9 percent increase for the pediatric population.

Gastroenterology was the most frequent prescriber specialty during the 12-month postexclusivity period at 70 percent compared to pediatrics at 2.6 percent.

Lastly, there was no mention of balsalazide in association with pediatric visits in an office-based physician practice survey.

The balsalazide pediatric exclusivity study consisted of a pharmacokinetic safety and efficacy study. It was a multicenter randomized double-blind parallel group eight-week study of two balsalazide TID dosing regimens. Sixty-eight pediatric patients, 5 to 17 years old, with mildly to moderately active ulcerative colitis

participated in the study.

Thirty-three pediatric patients were in the high-dose group that received 6.75 grams per day and 35 patients were in the low-dose group that received 2.25 grams per day.

The PK analysis concluded that pediatric patients 6 to 17 years old had lower systemic exposure to the two key balsalazide metabolites.

The primary endpoint was the proportion of patients with clinical improvement. Clinical improvement was defined as a reduction in the Modified Sutherland Ulcerative Colitis Index Total Score by at least three points, from baseline to eight weeks. The MUCAI assessment items include stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity.

The efficacy analysis showed that both balsalazide doses resulted in reasonable improvement for the primary efficacy endpoint but there was no statistically significant difference

between the high and low doses.

There was a 45 percent improvement in the high-dose group and a 37 percent improvement in the low-dose group compared to the normal placebo response rate for this class of drugs of approximately 20 percent.

In addition, for the secondary endpoints, the high-dose group consistently had better numerical scores compared to the low-dose group, but again there was no statistically significant difference between the high- and low-dose groups.

For the safety analysis, there were no deaths, four patients with serious adverse reactions, and four patient withdrawals due to an adverse event.

Overall, the conclusion was that the two dose levels were generally safe and well tolerated.

Out of the four patients experiencing a serious adverse event during the pediatric exclusivity study, there were two in both the

high- and low-dose groups.

Within the high-dose group, one patient had an ulcerative colitis flare and one patient experienced depression but had a prior history of depression.

Within the low-dose group, one patient had an ulcerative colitis flare and one patient had a clostridial infection in the setting of concomitant medications that included prednisone, Imodium, and Levaquin.

Out of the four patient withdrawals during the pediatric exclusivity study, there were one in the high-dose group and three in the low-dose group. Within the high-dose group, one patient had abdominal pain and urticaria. Within the low-dose group, one patient had frequent bowel movements, one patient had rectal hemorrhaging, and one patient had an ulcerative colitis flare.

Based on the pediatric exclusivity studies, the following seven sections of the drug labeling were changed.

To the Indications and Usage Section,

an indication for pediatric patients 5 to 17 years old was added. To the Dosage and Administration Section, the pediatric dosing of three 750 milligram capsules TID or one 750 milligram capsule TID was added.

To the Warnings and Precautions Section, an exacerbation of Ulcerative Colitis Subsection was added and this section included data from the pediatric exclusivity study.

To the Adverse Reaction Section, a Pediatric Ulcerative Colitis Subsection was added that described the adverse events and patient withdrawals seen during the pediatric exclusivity study.

The Pediatric Use Subsection was changed to note the other labeling sections that described the pediatric exclusivity studies, to note the pediatric dosing of 6.75 or 2.25 grams per day, and to note that safety and efficacy have not been established in pediatric patients less than 5 years of age.

To the Pharmacokinetics Section, a

Pediatric Population Subsection was added that describes the PK findings from the pediatric exclusivity studies, and to the Clinical Studies Section, a Pediatric Studies Subsection was added that describes the efficacy findings from the pediatric exclusivity studies.

Moving from the exclusivity study to postmarketing reporting, this table describes the adverse event reports during the postexclusivity period. For pediatric patients, there were three adverse event reports which comprised 9 percent of the total reports.

Of these three reports, two were U.S. reports. All of the reports were for serious adverse events with two being U.S. reports. There were no death reports.

Since there were so few pediatric adverse event reports during the postexclusivity period, the safety reviewer also assessed the pediatric adverse events since marketing approval.

For pediatric patients, there were eight adverse event reports which comprised 5

percent of the total reports. Of the eight reports, six were U.S. reports. Of the eight reports, six were for serious adverse events with five being U.S. reports. Again, there were no death reports.

Of the eight crude count pediatric adverse event cases identified since marketing approval, three of these cases were excluded due to miscoding of the suspect drug, indirect exposure via maternal use, or the event not being a serious adverse event. The remaining five cases involved serious non-fatal adverse events with direct drug exposure.

Out of these five non-fatal serious adverse event cases, there was one case of pericarditis, lower lobe pneumonia, and anemia that resolved after balsalazide was discontinued, one case of pancreatitis that resolved after balsalazide was discontinued, two cases of ulcerative colitis flares, and one case of thrombocytopenia that resolved with discontinuance of unspecified concomitant medications while

balsalazide treatment continued.

The presence of unlabeled adverse events prompted the safety reviewer to examine the drug labelings for other 5-ASA drugs. Whereas pericarditis, pneumonia and pancreatitis are unlabeled events for balsalazide, these events are included in the drug labelings for the other 5-ASA drugs as shown on this slide.

Consequently, the safety reviewer conducted an adult postmarketing safety review for balsalazide. Multiple adverse reactions reported in association with balsalazide were noted not to be included in balsalazide's labeling but were included in the labelings for other 5-ASA drugs.

Consequently, based on these pediatric and adult safety reviews, the FDA has requested a change to the Postmarketing Experience Subsection of balsalazide's labeling that would note that "the following adverse events have been identified during postapproval use of balsalazide: myocarditis, pericarditis, vasculitis, pruritis, pleural effusion, pneumonia, alveolitis, renal

failure, interstitial nephritis, and pancreatitis."

This completes the one-year postexclusivity adverse event reporting. The safety reviewer identified postmarketing adverse events in pediatric and adult populations that were not listed in balsalazide's labeling but are listed in other 5-ASA drugs.

Therefore, the FDA has requested the addition of identified adverse reactions to the balsalazide labeling and the FDA will send the advisory committee a labeling update via e-mail when the changes are complete.

The FDA also recommends routine monitoring of balsalazide for adverse events in all populations and asks whether the advisory committee concurs.

And in closing, I just would like to acknowledge the assistance that I received from FDA staff in the Office of Surveillance and Epidemiology, the Division of Gastroenterology Products, and the Office of Clinical Pharmacology.

Thank you.

Clarification Questions and Question to the Committee

DR. RAPPLEY: Thank you. Can you clarify for us if these changes have been made and accepted by the sponsor and already made in the label?

MR. ST. AMAND: Yes. Good morning. My name's Keith St. Amand. I'm the Medical Officer for the Division of Gastroenterology, and yes, the sponsor has submitted a changes-being-effected supplement which is currently under review but essentially accepts the recommendations that we've made.

DR. RAPPLEY: Okay. So, the question then before the committee is that the labeling have additions that include indication, dose, adverse reactions, PK data, and efficacy findings, and that they send to us by e-mail the exact language that would be included in that change, and then the second recommendation is that it move to routine monitoring, am I correct?

DR. MURPHY: We're recommending that these postmarket events that were noted during the pediatric review and then looked at overall, and actually this has evolved and we had a different question for you in the beginning, it's evolved, is that we -- the division and OSE and everybody over in Review basically came to the conclusion that we felt we should do it and the company has agreed to it.

So, the question at first was do you all think we needed to add this, but as I said, over time it's become clear that everybody views we should and so that's why the question now is are you comfortable with us just sending you these recommended changes or is there something else? I guess that's -- you know, if there's something else, we're not saying you can't tell us something else, but for right now, we are at the point where we actually have decided that we think this should be added to the labeling and the company has agreed.

So, do you agree with that or not?

separately identified as pediatric adverse events under Adverse Reactions and then we have a section on the Pediatric Use which just describes -- again, if it gets approved, what you're seeing here, if it gets approved, we just note in the Pediatric Use Section, you know, that you need to look at all these other sections because we want to make sure you go and look at the Dosage Section, the Indications Section, and the Adverse Events Section.

So that's why this information is spread out throughout the label because it was approved. So, did I help that question at all?

DR. WARD: Well, I think there's a Clinical Pharmacology Section where there was more details about the pediatric studies, and I didn't know whether that is proposed to be in the label or not.

DR. MURPHY: On Page 57, it's in the label.

DR. WARD: Okay.

DR. MURPHY: That is already in the

label, what we gave you. We really took to heart last time, we didn't have the most current label. So, we have the most current labels.

DR. RAPPLEY: But again, I think that points out the consistency of providing this type of information in the label which is something we strive for.

DR. MURPHY: Did you have anything else?

MS. VINING: I guess just a question for clarity. I noticed that there is no Phase 4 commitment on this drug and yet there is an acknowledgment that there will be a long-term use in pediatric populations of this drug, and I was curious why.

Is there any information that we might be able to get for the long-term use of this drug in the pediatric population?

MR. ST. AMAND: That's certainly something that we could consider. You know, I think at the time of the review, we were just trying to see if we could gather that information

through the postmarketing and concentrate on safety, but I don't know if you have any specific requests or if anyone else on the committee would have any recommendations for how to go about doing that.

DR. RAPPLEY: Any more thoughts? Dr. Cnaan?

DR. CNAAN: On Page 59 that Dr. Ward referred to, it says, it gives the response rates of 45 percent and 37 percent of improvement. What it does not give is the 20 percent placebo rate and in that sense, it gives a bit of a rosier picture than reality, given the placebo rate of improvement is 20 percent.

DR. RAPPLEY: I think the question that Mrs. Vining has raised is a serious one, whether or not we would recommend Phase 4 studies. So, I don't know if the committee's ready to think about that or speak to that.

Dr. Sandborg, do you have any feelings about that?

DR. SANDBORG: No, I was just

concerned. My question was really where did the 20 percent placebo rate come from? Was it from pediatric studies or was it from general studies in this population because it can be very different and there are different designs to look at for the future where the placebo rate can be directly measured.

MR. ST. AMAND: Yes, actually, you know, there were a lot of concerns, of course, with doing a placebo-controlled study in this particular disease. So that figure was actually taken from just our general experience with other products and some of that was adult studies. So, it wasn't a specific pediatric number. That was just to give us some basis with our review whether we were seeing enough of a treatment difference.

So, admittedly, not a data-driven with this study number that we had, so we didn't put that in the label.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Well, I guess I'm just puzzled and kind of disappointed that the label

suggests that efficacy has been established in children 5 to 17 years old when it hasn't, when the efficacy is presumably based on extrapolation from adults, but since there was no placebo group, I guess why does the FDA believe that efficacy was established in these studies?

MR. ST. AMAND: I think this was, you know, based on extrapolation. Again, these results were similar to the adult trials which we had and seeing similar response rates, I think, with the, you know, small population that we had to deal with, this was what we were able to come up with and again we don't have placebo-controlled data which would be the most desirable, but I think there were a lot of concerns with doing that type of study in this population.

DR. MURPHY: I think what you bring up is actually one of the areas Lisa and I have been talking about saying some more to you all today about extrapolation because there's a lot of interest in the work within the agency right now to bring more data, if you will, to the whole

field of when do we extrapolate, when do we not extrapolate, what is it that -- you know, how do we determine?

The law says that the course of the disease is the same, response to treatment is expected to be the same. How do you know that? What are the priors that you use to make those conclusions?

In this situation, what the division is telling you is that they felt the disease was similar enough and the law allows us to extrapolate efficacy from adults and in those situations, all we need to obtain is the dose and the safety data.

Now, we could have a whole discussion on there are different ways to do that. Sometimes the level of certainty as to the extrapolation is very solid. In other situations, they'll actually do exposure response studies first and others will just do PK studies.

So, it depends on where they think they are in their data, their evidence pool being

able to extrapolate, but fundamentally, the reason, the answer is they extrapolated the efficacy and that is a standard you can use.

DR. RAPPLEY: Dr. Bier?

DR. BIER: I don't think we're arguing about what you can do and what the law allows you to do. It's describing what we actually know and what was done, which is, you know, the data analyzed in this fashion suggests that it may be efficacious or, you know, support it. Saying it is efficacious, there's a -- you know, this carries a different message.

DR. MURPHY: Well, what we're saying is you either do or don't. You don't have a different class of it's efficacious or it's not. So, if you extrapolate the efficacy and what you're saying should we put in the label the basis of that extrapolation? Congress has actually asked us to look at that and to report to them on extrapolation, but you don't say that we think it's supported. It's either we think it's efficacious or we don't.

DR. BIER: Well, you know, I think there is this sort of legitimacy to saying something is efficacious and when I heard 20 percent placebo rate, I, you know, accepted that that was, you know, the sign of efficacy, but now I honestly don't know.

DR. RAPPLEY: Is it reasonable to say that this medication is efficacious based on extrapolation data?

DR. MURPHY: Yes.

DR. WARD: And is it the nature of the study with respect to the bridge is that we want to demonstrate exposure and that we have a dose in children to produce a percentage or a comparable exposure to that in adults?

Could I turn to the issue about the Phase 4 commitment, and I'm way outside my field as a neonatologist, okay, but what is the long-term natural history with respect to, for example, development of tumors or long-term toxicities from UC that might be either modified by treatment or that might be increased by treatment that should

or maybe shouldn't be looked for?

MR. ST. AMAND: Yes. I'm not sure that I can answer that question for you at this time. I don't know if, you know, that's something that pediatric gastroenterologists would have to help with, I think.

DR. MURPHY: So, I think what we're hearing from the committee -- again, Phase 4, a technical point here, Phase 4 commitments are made at the time of approval. So, this would no longer be a Phase 4 commitment. It would just simply be a postmarketing request for studies.

We're hearing from the committee that you are at least -- and we'd like to hear, Marsha, if everybody else in support of that or not, that we should consider, the agency should consider a longer-term follow-up study to look at longer-term safety outcomes from the use of this product in the pediatric population.

If I've misstated that, --

DR. RAPPLEY: So, would that be extending the postmarketing surveillance? Is that

how you would describe that? No?

DR. MURPHY: No, that's passive surveillance. So, I think what I'm hearing, at least Ms. Vining has said that she was looking for some sort of study and they come in all flavors, as you know, from -- we certainly would be looking at really more of a long-term follow-up study, I think, is what you're asking for. Correct me if that's wrong.

DR. RAPPLEY: Dr. Ward?

DR. WARD: From my perspective, recognizing there's a cost for that request in time and effort and money, I would like to hear from a pediatric gastroenterologist about the importance and need for that, based on natural history of UC, before making that a formal recommendation personally.

DR. MATHIS: I would also like to add that none of these medications that are used for ulcerative colitis are cures. This is a lifetime disease and so there are two aspects to this that one has to consider before asking for long-term

studies on one particular product.

One is, as Dr. Ward just pointed out, the natural history of the disease and whether or not there's been a large study to examine that and whether there's a difference if the disease presents in adolescence versus in adulthood, and then the other aspect is when there are chronic diseases where you have symptomatic care, you're going to have patients who are going to be exposed to multiple medications at different time points in the course of their life.

So, it's going to be very difficult to do a clean study on one product over the course of somebody's lifetime to find out what the long-term effects of a particular product are on a particular population.

I think Dr. Sachs reminded me that there is, of course, a lot of interest and this is something else that may warrant further discussion by this committee down the road, there's a lot of interest about doing disease-specific registries that would take into account multiple medications

used for the same underlying condition that may need to be considered by academia or other areas.

My point is that I think before we request a long-term study on a specific product, we really need to consider exactly what we would be asking for and whether or not asking for that study would actually address that overall question.

DR. WARD: There is a registry that is being undertaken. Our specialist in UC has been in discussion with us about whether to be involved or not. So, I know that there's at least something happening in that front.

MS. VINING: I would like to just hear from other people on the committee. When I read that there is going to be a long-term use of this medication for children, I think it's labeled 5 to 17 years old, it seemed that the fact that that was even in the materials begged the question what are we doing in the long term to figure out if this is going to have an impact on children into adulthood because they are going to be on it

so much longer than adults will be.

So, I would turn to the expertise on the committee to see if or how this might be something we consider. I don't have the answer, but I think that it's something worth considering.

DR. RAPPLEY: Dr. Notterman?

DR. NOTTERMAN: I think the idea of long-term evaluation of a drug that's going to potentially be used for the rest of the patient's life is a very good one.

I do think that, to follow up on Bob's comment about using our resources wisely, that we should learn from an expert what the experience is, if any, with other drugs of this class which may have actually some of the same active derivatives.

There may be more experience with this than we understand and so perhaps our recommendation could be that we learn more about this drug before making a formal recommendation.

DR. RAPPLEY: Dr. Farrar, did you want to add?

DR. FARRAR: Yes. Does the FDA have the capacity to do long-term studies of a single drug? I mean, earlier when we were talking about esmolol, they looked at sporadic reports and there were none.

I mean, I can see something with ulcerative colitis, you know, 20 years on this drug, no one's going to think to turn in an adverse reaction report 20 years later.

It seems -- do you all have the resources to even do these kinds of studies or should that be something that should be -- we should try to bring in some other agency or organization to work on?

DR. MURPHY: Well, let me be very simplistic about it. Do we have money to do these studies? No. Do we have capability to ask for certain studies? Yes, and it's the two modes that the committee is familiar with which is we can include it in the written request where it's part of the incentive program and one could say, well, why do we not ask for it under a written request,

or we can try to get the sponsor to do it under the PREA, when they come in for the same indication for a drug, and we can try to ask for those studies.

Again, the only real leverage we have is with the exclusivity because they don't get it if we don't ask for it. Now in that situation, you're also balancing if you ask for a very long-term study, you may -- you know, you're in the quandary of they never get their exclusivity, so they're not interested in it any way because, you know, it's too long for them to be able to get their exclusivity.

We've actually figured out some ways around that by for longer-term studies where we asked for the study to be enrolling and for them to bring in initial data and, you know, after a year or two and then indicate a commitment to the trial and then we would -- you know, we've been able to work through that sort of a conundrum with the exclusivity approach.

But otherwise, no, it is really our

ability to get the sponsors to do these studies that is the key to getting most of them done.

DR. RAPPLEY: So, can the agency work with the recommendation to seek further consultation about the utility of Phase 4 studies or long-term studies?

DR. MURPHY: Yes, I was sitting here trying to figure a way forward for this, and I think the thing to do is for us to do what I think everyone's comment is, not so much that you're saying we absolutely think you should do this but we think you ought to look at this and come back to us with what your thoughts are on what are the issues about a long-term study for children in this area.

So, we'll put that on our follow-up list to come back to you with that question. Do I have it now correctly outlined? Okay. Thank you.

DR. RAPPLEY: Okay. So, the agency will explore the utility or the reasonableness or desirability of a Phase 4 study around this medication --

DR. MURPHY: Yes, the pros and cons.

DR. RAPPLEY: -- and come back to us.

DR. MURPHY: We'll look at the reasons for and the reasons not to do it --

DR. RAPPLEY: Okay.

DR. MURPHY: -- and then we can look at potential ways of -- if there is enough in the pro side of this discussion when we come back, we can then also present what are some of the possible options and have some discussion on that, also.

DR. RAPPLEY: Okay. Very good. Then the last remaining question is do we accept the recommendation that this be moved to routine monitoring?

(Show of hands.)

DR. RAPPLEY: Anyone opposed? So, it's unanimously we accept that recommendation.

I would like for us to take our break now because we are moved a little bit -- we've run over our time a bit. So, we'll take a 10-minute break. I have right now it's 10:32. So, we'll

come back at 10:42. Try to stay on track and not eat into our lunch, so to speak.

(Whereupon, the meeting recessed at 10:34 a.m. and reconvened at 10:46 a.m.)

DR. RAPPLEY: We've been asked to extend the discussion of our last medication. There are issues that Dr. Newman and Dr. Bier would like to comment on a bit further. So, before we move on to our presentation by Dr. Sachs, we'd like to wrap this up.

Dr. Newman, do you want to start, please?

DR. NEWMAN: Yes, I just want to reiterate my concern about lack of a placebo group. This is a disease that we know waxes and wanes. We also know children often have a much greater placebo effect than -- than is seen in adults.

The endpoint for this study was a 12-point scale which was entirely subjective and so this -- the data from this trial really don't address the issue of efficacy at all. What we

know is, I assume we know is that the medication works in adults and that when you give it to children, sometimes some of them feel like they got better and that really isn't any data about efficacy at all.

So, I don't think we can say anything about efficacy in children based on this study.

DR. WARD: Can I argue with that? I think the scale used is an index of active ulcerative colitis symptoms and disease, and I recognize there is a 20 percent placebo effect that has been extrapolated, but it looked like during this monitoring phase, there was like a 69 percent improvement in those scales.

So, I actually think we do know something about it. Unless I've misread the data which is altogether possible.

DR. RAPPLEY: So, I would like to just clarify, then, what point we are discussing right now and that we could have perhaps another five minutes to discuss this and that point is that the current language, Dr. Newman suggests

that, the current language is too strong in indicating efficacy of this medication and needs to be changed. Am I correct? Okay.

So that's what the discussion will be about then for the next five minutes. And -- other comments?

DR. MURPHY: I want to say a couple things first. Number 1. I think that if there is an issue, that this is a division that deals with these products and this class of products and they felt that the endpoint just was an appropriate endpoint and they did do endoscopic I mean -- also measurements.

So, I think when we present these trials to you, we are trying to make sure that we've reviewed the safety part that's coming out of the trials.

What we did not bring to you, and again we're glad to entertain the comments, but I just want to say that we didn't bring to the committee do you think this product was efficacious or not?

This was not a review because we would have brought a whole lot more to you so you would better understand what was done if we were asking you about the efficacy of the trial.

So, having said that and having said this not an all-day meeting where we are presenting all that information to you, I'm asking you, I'm telling you in a way that what you saw or what was decided was efficacious was the division's accepted standard of endpoints.

Now if you disagree with the endpoints and you think that they need to have different endpoints, then that is a different discussion, but for right now, what we're telling you is that these are the standards that they used.

Now, -- and that they thought that they had enough evidence of response that they could extrapolate the efficacy. So, there's two things. Do you disagree with the endpoints? The second thing, do you disagree with the extrapolation? So, those are two different

questions.

DR. RAPPLEY: Well, I think we earlier said that we just want to see it acknowledged that it was extrapolated. That would be the important point.

Is there more comment on the first?

DR. CNAAN: I have less discomfort with endpoint because I've seen several studies in this area with this endpoint and it seems to be reproducible and reliable, despite what it looks like on the face of it. So, I'm not that much concerned with the endpoint.

I'm actually more concerned with the design. I understand that it's probably no longer ethical at this point to do a placebo-controlled design in this set-up. However, that might be because there are active controls.

So, my only suggestion is again to go back, as was said before, and put some thought into it. Can we get some better data so that we won't have the discomfort that Dr. Newman is expressing and that I share that the statement

right now appears too strong, at least from what we are seeing?

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: I just want to comment on the ethics of doing a placebo-controlled trial. Again, this is a -- the children had mild to moderate ulcerative colitis. It's a disease that waxes and wanes anyway.

If we accept that 20 percent historical placebo response rate which I think actually is pretty meaningless because it's a different endpoint and it's adults rather than children, but if we accept that, then the difference between that and the lower dose group was a 17 percent difference, 37 percent versus 20 percent, which means that for eight weeks, one patient out of six would have been deprived of that level of 3 point out of 12 benefit, and since we actually don't know at all what the placebo response rate and a 40 percent placebo response rate is entirely plausible for this endpoint in this disease, I think the answer is that we don't

really know whether this medication has any efficacy and therefore it is ethical to do a randomized trial.

There's only eight weeks in a disease that will be lifelong and they may be on this medicine for years. So, I think it's worth finding out, spending, you know, placebo for eight weeks to find out whether it actually works.

DR. MURPHY: Okay. So, now you have another question on the table, which is really -- and again, we didn't come to talk about the efficacy design trial, but you are saying that the whole issue of doing a placebo-controlled trial is ethical and I would agree, but you are saying that you think that needs to be reconsidered.

So, you are telling the division that you think you need to reconsider the whole trial design as to whether these placebo-controlled trials should be done and also you have to do it in the context of they are saying they don't need to do that.

DR. RAPPLEY: So, may I suggest that

--

DR. MURPHY: I think that's something we have to -- is it ethical to do a controlled trial when you don't think you need to do it is another part of the question. So, we have to work through that, too.

I'm looking at Skip, but I'm not going to ask him to come up and answer that today. Okay? But that would have to be thrown into this discussion.

DR. RAPPLEY: May I suggest that we ask the agency to take these concerns that have been expressed today and to consider them and to report back to us on how that fits in with your context of your usual approaches to these types of medications and then we can comment on whether or not we think that process needs to be adjusted?

DR. MURPHY: You are fundamentally asking us to bring the whole issue of how trial designs are conducted in this disease.

DR. RAPPLEY: Well, maybe we could --

DR. MURPHY: And that --

DR. RAPPLEY: -- put it up a --

DR. MURPHY: -- is an advisory committee unto itself.

DR. RAPPLEY: Well, but maybe we could put it up a notch and just say, you know, in chronic disease, the committee has raised some concerns about how we do efficacy studies and how we do Phase 4 studies. Is there -- are there other ways that we could think about moving forward that we could begin to look at the special issues that are presented by chronic disorders in children?

DR. WARD: This goes back to '94 Rule that allowed extrapolation of efficacy when the disease process is similar, and I really thought UC starting in childhood had a very similar course to that in adults and this would be a discussion almost going back to laws that have been now on the books for quite a long time.

DR. RAPPLEY: But maybe that is what we need to be reminded of, is how these approaches came about and then why they are still relevant to

the diseases that we're discussing or how we might shape them in the future.

Dr. Bier?

DR. MURPHY: We do learn as we go through this process, and I don't mean to say that you shouldn't be having this discussion. I'm just trying to explain the breadth of what that discussion is going to be because it's fundamentally saying that we think we need to discuss whether you can extrapolate, we need to discuss if we think you can't extrapolate because if you can't, it would be very hard ethically to do a trial, okay, that then you're enrolling children into something you don't need to, but if you can't extrapolate, can you do a placebo-controlled trial and what are the endpoints?

So, I think there's -- that's a whole discussion -- long discussion that we would need to bring to the committee.

DR. BIER: As long as the conclusion is it is efficacious, there is no leverage to doing a study. I mean that's -- if the conclusion

is we don't know if it's efficacious, then there is leverage for doing a study.

DR. MURPHY: Yes, and I think that is the whole point. We have to go walk through the issue of the division has made the cut that they have extrapolated efficacy. So that is what the committee is saying. They don't know that they agree and if we do that, because once you have made that extrapolation, you don't need to prove efficacy, you are simply proving -- you are defining, excuse me, defining the dose and defining the safety and that is how the law is written.

So, what the committee's saying is we don't know that we agree with extrapolation in this issue. So, we have to -- and I guess it might be helpful, Marsha, to have us better understand is that -- is it a consensus of all the members or a lot -- some of the members because we need to put this in our priority list somewhere. So, I'm trying to get a feel for the extent of the concerns from the committee.

DR. RAPPLEY: So, I think it also needs to be placed in the context that as you -- as we as a society have evolved to acknowledge the special conditions and circumstances of children and medications, and we now have made some really important steps forward and are learning some very important information that we previously did not have access to, we have raised the bar ourselves and we are demanding more and more, as you are of yourself as an agency.

So, I think it's not surprising that we begin to question the premises on which we have approached these medications historically. We also don't want to send people off track and move away from examining the medications that are important for us to consider as we revisit things over and over again.

So, I think your point is well taken. So, is it -- I'd like a sense from this committee then where we would like the agency to go with this concern about both extrapolation and long-term studies for chronic illness.

Is this something you want them to reflect on and come back and recommend or review with us how they address this and then put it out as some kind of special consideration or is this something that you want further two-day conferences on?

DR. WARD: Can we separate those two issues? Long-term studies and extrapolation?

DR. FRANCIS: Just one small comment. There have been a number of people within FDA looking at those issues, particularly long-term studies and how it fits into the regulatory function, and one of the things that's come up, you may have heard of, is the Reagan-Udall Foundation, should be sort of a related cousin to what the NIH Foundation is to NIH, where issues that normally the particular agency can't do will have a foundation where you can work out how to do some of these studies in collaboration with private industry, investigators like yourself or others to look at some of those issues.

So that may be actually a vehicle to

look at some of these things in a more systematic way and time.

DR. RAPPLEY: And maybe that whole set of opportunities are not well known to us and it would be part of what you could present to us in terms of how to approach these things in the future.

DR. MURPHY: And it is a brand-new process. Does it have funding?

DR. FRANCIS: No, the concept has been approved, the funding is what they are working on now, and they have the executive board's been appointed and the last I heard, within the next two years, it will start being operational.

DR. RAPPLEY: We are familiar with those unfunded mandates.

DR. MURPHY: I think Bob asked to separate the issues. I think that would be helpful to us because extrapolation is something that we are struggling with and long-term studies are something that we are struggling with, not --

and mostly to do with some of the chronic diseases but not always, you know. There may be reasons we need long-term studies for other chronic diseases.

So, if you would maybe approach this separately for the committee to give us some feedback as to what their concerns are in those two areas?

DR. RAPPLEY: Dr. Sandborg?

DR. SANDBORG: This is a comment about the extrapolation issue. There may be differences between diseases where you can extrapolate easily or not easily, and I think chronic illness is an area where the actual study in the moment, the study design, how it is actually conducted, has a huge effect on the placebo rate in chronic illness because of the variability in reporting and the -- some of the measures which are more subjective than others and all the aspects of why people do better, even on placebos in controlled trials, is very true in children as it is in adults.

Whereas for other drugs, extrapolation may be much more straightforward and so there's a possibility that you may want to parse that out, the different types of drugs or different types of studies, and then there are different study designs that can have a placebo phase or an active comparator or something which is not as ethically challenging as a full placebo-controlled trial but may be, especially in these chronic illnesses where you really do need that, may be acceptable.

DR. RAPPLEY: So, I would like to suggest then that the agency take some time at our next meeting to concisely address how they approach the decisions around extrapolation as one subject and then decisions around chronic conditions of children as a separate subject, and we could at that meeting then, knowing that that information is coming and reflect on it between now and then, give you feedback about whether or not we think that needs to be revisited in some way or discussed further.

DR. MURPHY: Well, this is quite timely, actually. We just have a new working group, Dr. Rodriguez is the -- and Dr. Julia Dunne who, and I didn't plant this, honest. I don't know. I had nothing to do with this. This is actually quite unexpected from the committee today, have actually sent letters to a number of the division directors asking them, particularly those divisions where we know we do do extrapolation, to participate in a working group, and Dr. Dunne is with us for three years from the regulatory -- English Government regulatory agency and so we are also bringing their perspective into this and they will be looking at this issue.

So, if we come back this year or at the next meeting, we are not going to have any definitive answers and I actually think that's preferable. I think it would be preferable to bring back to you where we are beginning to outline our thinking on this and get some of your thoughts on some of your issues.

So, as you said, it would be a good

idea for you all to be thinking about this. We can try, Carlos, to send them in the meantime some information so it's not coming at the -- right before the meeting on the law as far as extrapolation is concerned.

We have actually had some presentations where people -- different division directors have talked about extrapolation, why they've done it, why they haven't. We'll see how much of that is public and we'll try to send you some of that information in between for your reading pleasure.

DR. RAPPLEY: Is the committee agreeable to that? Okay. I think we do need to move on. We have medications that we have postponed addressing and we need to move to that, and if people feel that it is very important to continue this discussion, would you approach me at lunch and we will make plans thereafter?

Thank you.

Suprane (desflurane)

Standard Review of Adverse Events

DR. SACHS: It's nice to see everyone again.

I am Hari Sachs in the Pediatric and Maternal Health Staff.

I also want to acknowledge Dr. Schultheis -- Lex Schultheis sitting over at the table from the Division of Anesthesiology, and at the risk of putting you all to sleep after this quite energetic discussion, I'll be discussing the adverse events for desflurane.

Just in case you need a reminder, here is an outline of the talk.

Desflurane is marketed by Baxter as Suprane and it is a general inhalation anesthetic that was originally approved in September of 1992. Pediatric exclusivity was granted almost 14 years later, on September 13th, 2006, with labeling changes primarily related to safety approved in December of the same year.

In adults, desflurane is approved either for induction or maintenance of anesthesia during both in- and outpatient surgery. However,

in pediatric patients, desflurane is only indicated for intubated patients that require maintenance of anesthesia who have been induced by other agents and this is due to the high incidence of respiratory adverse events.

The dosage is individualized based on the patient's response and there is dosing in the labeling down to age 2 weeks based on mean relative potencies.

Not surprisingly, desflurane is primarily used in the inpatient setting and the majority of use is in adults with desflurane accounting for almost 40 percent of discharges. There is similar use actually for sevoflurane and pediatric use of the product is limited to less than 3 percent which accounts for approximately 2,900 unprojected discharges per year. There really haven't been any trends or changes in use in the time frame that we will be talking about.

Okay. Let's look at the exclusivity studies. Now before the studies were started, desflurane was already approved for maintenance in

intubated patients and therefore the studies were designed to just look at the safety and tolerability in non-intubated patients and originally the written request asked for studies down to neonates.

However, as you will see, there was such a high incidence of respiratory adverse events in the youngest age cohort, that the written request was amended and what ultimately was done was a study -- a single study in 400 children, ages 2 to 16, which randomized 3:1 for these patients to receive either desflurane or isoflurane via laryngeal mask airway or face mask.

Despite the lower dose of desflurane that was used, there was higher adverse events noted in the desflurane arm, particularly in the 2 to 6 year olds, as well as all the earlier discontinuations were noted in that arm, and more patients in the desflurane arm required treatment intervention.

So, as a result of these studies, the labeling was changed under the Clinical Trial

section in Pediatric Surgery to emphasize that desflurane is not approved for maintenance of anesthesia in non-intubated patients and these findings are reiterated in the Indications and Use section as well as the Respiratory Adverse Reactions are really highlighted in the Warnings sections of the labeling.

And as you can see under the Pediatric Use section, the percentage of adverse events has been moved and just to put this in a little perspective, I'm not an anesthesiologist, but my anesthesiologist colleagues tell me that the incidence of laryngospasm from many other agents is on the order of 10 percent, but you can see here that the incidence is about 50 percent.

In addition, although not shown, the respiratory adverse events are broken down by age for the patients that are non-intubated as a result of the safety study.

Now I'd like to just highlight some of the adverse -- I mean the additional safety concerns that are found in labeling. Desflurane

is contraindicated to patients who are sensitized to halogenated anesthetics because of the risk of hepatitis and warnings include the risk of perioperative hyperkalemia, malignant hypothermia, and the need for desflurane to be administered by skilled personnel in a monitored setting.

Note that perioperative hyperkalemia, albeit rare, has led to cardiac arrhythmias and death during the post-op period, particularly in patients with underlying neurovas -- neuromuscular disorders, such as Duchenne muscular dystrophy; concomitant succinocholine has also been noted with many of these patients.

And there are features that are suggestive of rhabdomyolysis, that is elevations of CPK and urine myoglobin, which are noted along with the hyperkalemia.

The precautions list the potential for dose-dependent hypotension and tachycardia as well as special recommendations for particular patient groups, such as patients undergoing neurosurgery or cardiovascular surgery, and the

need to adjust the inspired nitrous or air concentrations so that adequate oxygenization is maintained is also outlined as well as the risk of hepatitis if the patient is sensitized.

Common adverse events include headache, cardiac rhythm changes or hypertension, gastrointestinal upset, increased salivation and conjunctivitis, as well as all the respiratory adverse events you have seen.

Rare hepatic failure can be noted as well as transient elevations in white count and hypoglycemia.

Okay. Let's look at the adverse events that were seen and since market approval, you can see there has been almost 630 reports in patients of all ages and most of the events are serious. When you look at children, there's about 47 and this is the raw count which is 7 percent and that does slightly exceed the use.

Most of these events were serious and five of them, and again this is raw counts, were associated with fatalities, but I do want to point

out that when we looked at the amount of unduplicated cases, there is actually 33 cases that relate to pediatrics and three fatalities.

Now the details of the fatal events are provided on the next several slides. There is a 9-year-old whose only past history was that of anemia, who was undergoing leg surgery. She was induced with methohexital and isoflurane and switched to desflurane partway through the case, and at some point, and it is actually unclear from the record exactly when, whether she was switched, you know, because she was getting hypoxic or she became hypoxic after she was switched, she became hypoxic and bradycardic and arouse were noted on her exam, pink frothy fluid from the ET tube, and even though she did respond as far as vital signs go, unfortunately six days later, she died from hypoxic brain injury.

The -- notably, all the labeling for the agents she received does include respiratory depression, hypoxia and tachycardia.

There was also a 5-year-old who had

meningomyelocele who received desflurane as well as several other anesthetics and died 18 days after surgery, after having rhabdomyolysis, and his CPK was fairly remarkable.

Note that the labeling, as I mentioned, for desflurane does describe elevations of CPK and urine myoglobin which are consistent, although the term "rhabdomyolysis" is not used, but the labeling for propofal does specify that rhabdomyolysis may occur.

And the last case which did occur in the one-year, five-year -- one-year postexclusivity period describes a 5-month-old who had a fatal respiratory arrest seven hours after receiving anesthesia for an incision and drainage of an abscess that was associated with vaccination.

The question was raised about an underlying mitochondrial disorder because on autopsy, the child had an unusual necrotizing myopathy and labeling for all the agents does describe, of course, the need to administer in a

monitored setting and the risk of respiratory suppression, particularly for desflurane.

So, speaking of the one-year postexclusivity period, based on crude counts, there were approximately 42 reports in all ages and when we focus in on the pediatric reports, six of these, which is 14 percent, also seems to be a little high, but when we look at the actual hand-on review, there is actually only two unduplicated cases and one of them was this fatality you heard about. It was actually reported three times.

So, in addition to that fatality, there was a 2-year-old who was undergoing surgery for an artificial valve and she developed a prolonged coagulation time. Among the medicines she received was an anticoagulant, I won't hesitate to pronounce it, and even though the anticoagulation therapy could have been related, as you know with hepatic dysfunction, you can see abnormalities in coagulation, so it is certainly not clear if the anesthetic could have contributed.

Due to the small number of adverse events during the exclusivity period, the safety reviewer, thank you, Peter, went back and looked at all the adverse events in children and they are summarized on this slide.

Most of the events, actually the majority, are related to labeled events or are labeled and certainly all of the events did occur in patients who had multiple illnesses or concomitant medications and were highly confounded, but as far as the serious respiratory events, there were cardiac arrests and seizures that occurred in more than one patient and there was one case of pulmonary edema and I will describe those for you.

Now three patients experienced a non-fatal cardiac arrest and as you can see, two of the patients, the first two, experienced cardiac arrest that was temporally related to a respiratory adverse event. The first patient had laryngeal spasm, the second patient had hypoxia, and, of course, this is germane because

respiratory arrest in children is the most common cause of cardiac arrest, at least that is what they drummed into me when I take my PALS classes.

The last event was an adolescent with Duchenne muscular dystrophy who had a related cardiomyopathy and developed ventricular arrhythmia and cardiac arrest after general anesthesia and that anesthesia did include desflurane.

Note that the labeling for desflurane does not explicitly mention cardiac arrest, although there is certainly warnings about respiratory failure and the need to adequately monitor these patients and be prepared to intervene.

But, you know, the safety reviewers did look further and they looked at cardiac arrest cases for both pediatrics and adults and there actually seems to be a signal for cardiac arrest in adults as well as kids and also for the whole class. So, there is a suggestion that the labeling here gets revised.

There was another unlabeled event, a case of pulmonary edema in an 8-year-old, although this event does seem to be related to the fact that this child emerged quite rapidly from anesthesia, bit and kinked his airway and then developed the pulmonary edema. They think a vacuum was created.

The pulmonary edema, while not described in desflurane labeling, is described in the labeling for the other agent he received.

Finally, two patients developed seizures which is also an unlabeled event. One was a 6-week-old who had seizures during a pyl -- following a pyloric stenosis repair. He did recover after treatment with an anticonvulsant, and then there was a 16-year-old, male, who had tonic-clonic seizures and transient blindness while receiving multiple agents during arthroscopy.

Now, as I said, desflurane is not labeled for seizures but methohexital, which this child received, is and blurred vision is also part

of the fentanyl and alfentanil labeling. So, you are kind of left with one case in a 6-week-old that might be related.

The remaining cases, as I mentioned, were really confounded by multiple medications and/or related to -- I mean and were clearly labeled, so I won't discuss them.

So, in summary, the labeling does state that desflurane is not recommended for use in induction and that has actually been the case before the exclusivity studies were done. The labeling was updated to reflect that it is not approved for maintenance of anesthesia in non-intubated patients.

The adverse events have been incorporated, the respiratory adverse events, and although it is not explicitly described in the labeling, there has been several cases of cardiac arrest that were reported since marketing approval in both adults and pediatric patients and for that reason, FDA is recommending that the labeling be revised to include cardiac arrest as an adverse

event.

I do not think there has been specific enough discussions that we have proposed labeling, though.

FDA recommends routine monitoring of desflurane for adverse events in all populations, if you guys concur, and before I let you all start the discussion, I do want to acknowledge the contributions from a very diverse group of folks and a lot of hard work behind the scenes.

Clarification Questions and Question to the Committee

DR. RAPPLEY: Thank you. So, two recommendations. One is that the labeling be changed to include cardiac arrest as an adverse event, and then the second recommendation is that this medication be moved to routine monitoring.

Discussion on the first recommendation?

Does the committee feel this is an appropriate addition to the label? Is anyone opposed? So, unanimous in that.

Does the committee feel this should be moved to routine monitoring? Anyone opposed?

DR. NEWMAN: I guess I'm puzzled. It seems like this medication is a lot riskier than isoflurane, at least in children, and really high incidence of respiratory adverse effects and no suggestion of any greater efficacy.

So, I'm wondering why would it not be contraindicated in children. Is there some reason why one would ever want to give this riskier medication, medication riskier than isoflurane to kids?

DR. RAPPLEY: Yes, Dr. Notterman?

DR. NOTTERMAN: I was actually going to make the same point. I was going to phrase it differently and ask if we could have some clarification on how the agency decides the balance between non-approval and contraindication.

I would have come down, if there was that kind of process, on the side of contraindication in this age group.

DR. RAPPLEY: So, currently, the

label is if they do make a distinction between induction of anesthesia and maintenance of anesthesia.

DR. SCHULTHEIS: Well, there are differences in risk for isoflurane and desflurane. Desflurane is less metabolized than isoflurane and there may be circumstances when the anesthesiologist would prefer to use a drug that would not be as hepatically changed in children.

Certainly the concerns with regard to respiratory adverse events is primarily with regard to non-intubated patients. That's what the labeling changes, the recent labeling changes addressed and so there are certainly times when it would be considered for use in intubated patients as well. So that we wouldn't contraindicate it entirely for that group of patients.

There's always a risk-benefit with any combination of drugs and it may come down to such variations in such things as cardiac- loading conditions, metabolism, rate of recovery from anesthesia, that may be important to assess, say,

neurologic function, things like that.

DR. RAPPLEY: Dr. Notterman?

DR. NOTTERMAN: Thank you for that, and I was actually referring specifically to non-intubated patients and I was wondering if it was possible to contraindicate that particular use but not its use in intubated patients.

DR. SCHULTHEIS: Again, the choice may come down to other conditions, other aspects of the risk-benefit profile, like rate of recovery, and even in a non-intubated patient, it may be preferable to have a more rapid emergence for evaluation of neurological function, for example.

So, you know, I hesitate to say that we could contraindicate it when there are certain potential advantages in certain patient populations to one drug versus another.

DR. RAPPLEY: So, the agency has reviewed the indications --

DR. SCHULTHEIS: Yes.

DR. RAPPLEY: -- and feel that there

are special circumstances --

DR. SCHULTHEIS: Yes.

DR. RAPPLEY: -- under which the risks may be tolerable?

DR. SCHULTHEIS: Right.

DR. RAPPLEY: Yes?

DR. MATHIS: I would just like to add to that, that remember that the bar for a contraindication is that there would never ever be a situation where the benefit would ever outweigh the risk.

So, if there are clinical situations where a physician might think there was benefit to using this product, then a contraindication wouldn't be appropriate in the pediatric population, so that to never ever use this product in pediatrics.

DR. RAPPLEY: Okay. So, are we -- we've endorsed then both of those motions to -- both of those recommendations to add cardiac arrest as an adverse event and to move this to routine monitoring? Anyone opposed?

DR. KOCIS: I'm sorry.

DR. RAPPLEY: Dr. Kocis?

DR. KOCIS: I just want to continue to follow up. I'm still confused on the exact wording on not approved versus more serious in the non-intubated patients because, as it's labeled here, it's not approved versus --

DR. RAPPLEY: What page are you on?

DR. KOCIS: 243. I guess I would see it more for during maintenance in intubated patients for -- again, I'm not an anesthesiologist, but I can imagine that there would be reasons that you suggested, but as far as, you know, that risk profile in induction or the maintenance in the unintubated patients seems excessive and to say it's not approved versus contraindicated, I'm still unclear about whether we should change the labeling to make it more strong for the non-intubated patients.

DR. MURPHY: Page 237, and see if this is addressing because when you go -- in the beginning, you know, of the label, you come to the

Indications and Usage Section and so what you're saying is you think the -- the Indications and Usage Section says right up front it's not recommended for induction in pediatric patients.

So, you and to go ahead and see the, you know, different Precaution Sections about that. I'm trying to find the other Precaution Sections.

DR. RAPPLEY: It also says after intubation that it's indicated for use. Your question, Dr. Kocis, is should we make that language stronger? Response?

DR. SCHULTHEIS: All I can say at this point is we've already had that discussion internally and we determined that there were cases when it might be preferable to use desflurane as opposed to other inhalational agents, even when the patient is non-intubated, and that again may have to do with rapid emergence, ability to assess the patient, hepatic insufficiency, and so forth.

DR. KOCIS: And again not being an anesthesiologist, I just would argue I can't

imagine a reason when there are alternative agents to use or to intubate a patient. So, I can't imagine the scenario where I wouldn't intubate the patient for the use of desflurane or you wouldn't use another agent in the unintubated patient, but again I don't do that for a living, but these, you know, adverse events are, in my opinion, very severe in nature and certainly could have been catastrophic. While they may not have been, in many of the circumstances they certainly could have been.

DR. RAPPLEY: So, I do think that these are very important questions that we are raising, but we are also then suggesting that we revisit a decision that has been made and that would require a diligent discussion and review of information that would be probably a half-day session, and I think again if someone feels strongly about that, strong enough to think that we need to move to some question of that nature, then we need to bring that to the attention of the agency, but otherwise we need to act on the

general pediatrician, you have a child that has an abscess that's bad enough that it needed drainage, I mean one could wonder if the kid simply got septic.

There's not any details in the record to support that, but there's certainly no details in the record to say that's not the case.

I think that the finding of the necrotizing myopathy is also pretty interesting and the folks that, you know, published the case actually wondered about whether or not this child had an underlying abnormality that may have predisposed him to react funny to the anesthesia.

Unfortunately, they also said that, at least at the time, there wasn't the way to check postmortem for that more -- you know, whether -- what mitochondrial defect he might have had. There wasn't a way to check.

DR. BIER: If they had tissue that wasn't preserved, they had DNA and they can in fact check mitochondrial DNA abnormalities.

DR. SACHS: All I can tell you is

what was in the reports.

DR. RAPPLEY: Does that answer your question, Dr. Daum?

DR. DAUM: It tells me that there really is no answer to my question.

DR. RAPPLEY: It's not the case where we have access to either the patient or the specimens afterwards as an agency or as a committee. So, we really have to rely on what's reported and what decisions are made at that point in time.

DR. DAUM: Yes, and my cynical side says at least they didn't blame the vaccination.

DR. RAPPLEY: Well, we don't know that. I doubt that, actually.

DR. BIER: I realize that it isn't our job to deal with that, but from the perspective of pediatric counseling to the family and their other children and whether they have another child who may, you know, need to undergo anesthesia, I mean, this is a critical issue that, you know, at least some data could have been

we understand what it is that you think should be --

DR. KOCIS: Right. And it's semantics to some degree, but we've talked about how neutral or negative we can be with changing one word or the other and not approved for kids is like everything and then when we contraindicate something, then we don't use it, and I guess that would be my concern when we say it's not indicated or not approved. It doesn't mean that anesthesiologists wouldn't use it, and again if there was no alternative to not using it, I guess I would leave that more open than when seemingly for somebody who doesn't do this for a living alternatives that seem to have less risk, that why wouldn't we say it should be contraindicated or not -- rather than not approved?

So, I guess that's where I'm going with how strong of a negative versus a neutral we're going to be.

DR. MURPHY: Okay. So, your question was really not changing the not recommended but

it's the changing the not approved from maintenance in the non-intubated to a contraindicated and you heard the answer to that. So, the answer is that at this point the agency deliberately did not move it into the contraindicated.

So, I just want to make sure we're all talking about the same thing.

DR. KOCIS: And all I can say is from what data we have, I wasn't at the discussion, I'm sure other people were and could explain that to me, but I couldn't see why -- I would advocate that they -- I at least want to understand why they wouldn't have said something more seriously and I guess to pose the question of would they reconsider their recommendation?

DR. RAPPLEY: Dr. Notterman?

DR. NOTTERMAN: Is this a case in which additional surveillance and an additional report might be the appropriate response?

DR. RAPPLEY: Rather than routine monitoring? Comments from the group?

DR. WARD: Marsha?

DR. RAPPLEY: Sure.

DR. WARD: One of the things I think we have to keep in mind is what Dr. Mathis said, that the regulatory hurdle for contraindicated means there is no use for this, and I would -- I think not being again an anesthesiologist, I think I would want to defer to anesthesiologists, that there may be a clinical setting in which rapid emergence is important, more important than the issues around airway irritability, that they are trained to deal with.

DR. RAPPLEY: So, does --

DR. MURPHY: I guess what we're asking -- can we change our question?

DR. RAPPLEY: Certainly.

DR. MURPHY: Well, in a way it's the same question, but what we hear is there's concern about this product with the present labeling. Okay?

What if we changed our question to we continue to monitor and come back to the committee

with the present labeling versus taking the recommendation of changing the labeling at this point?

Could I pose the question, Marsha, for you to pose to them that way?

DR. RAPPLEY: Certainly. So, the question then is do we recommend continued monitoring and a return to this committee then with that new information and the committee's -- the agency's recommendation then about whether or not the agency feels the change is then needed, indicated?

DR. MURPHY: Yes, thank you, that's the question.

DR. RAPPLEY: Okay. Dr. Newman?

DR. NEWMAN: I am not sure that continued monitoring and sort of the case reports are going to be that helpful and I guess I just would wonder whether -- I mean, the current labeling under Indications, it just says Suprane is indicated for maintenance of anesthesia and these are after intubation in infants and

children, and it just seems like that doesn't really capture the data, that it should just be special circumstances.

It should be indicated as a second line choice or as when there is some compelling reason not to use a safer alternative, but to just have it just say after intubation, it's indicated, I don't think captures the pretty big difference in safety between it and alternatives.

DR. RAPPLEY: Other comments or thoughts? So, Dr. Newman, your position is that no, that's not adequate? You want to see the labeling changed?

DR. NEWMAN: Yes.

DR. RAPPLEY: Response from the agency?

DR. MURPHY: I guess we would say that we just prefer to see how everybody else feels. In other words, I agree, I understand the limitations of what you're saying, but I do think that we have had situations -- because the thing that's striking about these cases is these kids

were really basically healthy kids, I mean in a couple of these.

So that's why you've got such a presentation today. So, I do think that continuing the discussion of the committee, that we think that we'd like to change our question to the way I said it and we'd like to hear if other people fall on the side of doing that or they fall on the side of Dr. Newman's suggestion of no, I want it changed now.

DR. RAPPLEY: So, we've heard discussion about would say no, that's not adequate to continue monitoring.

Is there discussion about the adequacy of continuing monitoring at this point in time?

DR. MURPHY: And again do look at the Indications Section because it does refer you back to all the precautions and stuff.

DR. RAPPLEY: Dr. Cnaan?

DR. CNAAN: I guess I would favor the suggestion by Dr. Murphy on looking at Page 237,

at the Contraindications, and it does rise to the level of never, and I guess what we've heard is the logic of don't put it in the contraindication unless it's never.

So, I would like to see, be another year, I don't know what, but some period before going to the extreme of never.

DR. RAPPLEY: Dr. Notterman?

DR. NOTTERMAN: I also agree with the suggestion of continued monitoring. I'm reluctant to make a recommendation to move this into contraindicated status, even for a limited circumscribed indication, without more information from expert practitioners and scholars who work with that, and we don't have that expertise.

DR. RAPPLEY: Dr. D'Angio?

DR. D'ANGIO: I'd agree that continued monitoring sounds reasonable at this point, but it does sound that at some point as if we're going to need to spend a significant amount of time talking about this and perhaps the next time it comes back, it would be reasonable to

devote a significant amount of time to the reasoning behind the previous decision with the additional data that we'll have at that point.

DR. RAPPLEY: Are we ready to take a vote on this? Yes, Dr. Newman?

DR. NEWMAN: I just want to clarify. I'm not saying that it should be contraindicated. I'm just saying that the indications should be narrowed somewhat to reflect the data that was done, you know, that's described under Pediatric Labeling, that it's significantly less safe.

So, it's not contraindicated but it's only indicated when there's some reason to use it rather than a safer alternative.

DR. RAPPLEY: So, there are two suggestions. Well, the first question that has been posed to us is to continue monitoring this medication and to come back to the committee with a recommendation based on information that will come from that further monitoring.

So, I'd like to call a vote on those in support of that particular suggestion, that

question.

What members of the committee support continued monitoring and returning to the committee with the new recommendation for labeling?

(Show of hands.)

DR. RAPPLEY: Opposed?

(Show of hands.)

DR. RAPPLEY: So, I see three opposed. Okay. All right.

Dr. Pena, can you give us a count? We need to see the hands again.

DR. PENA: Yes. Can we see a show of hands again that we can do a count on?

DR. RAPPLEY: Those in favor of continuing monitoring and returning to the committee with a recommendation?

(Show of hands.)

DR. PENA: 10 are in favor of active monitoring, three are not in favor.

DR. RAPPLEY: And one abstention. Three are -- well, I think what we have to say is

three are not in favor of that particular motion.

Make a further motion that we return to routine monitoring.

Okay. Does the agency understand the will or the recommendation of the committee?

DR. MURPHY: Okay. So, well, I want to get to the three. One second here.

So, the majority of the committee is recommending that we continue to monitor the situation, to bring back to you -- and it may not be a year, if we don't have enough cases or it may be a little longer till we think either it's futile or we think we have enough more normal kids who are having severe problems that we'll come back to you, okay, but we will definitely come back within a couple of years with additional information.

In the meantime, you would like us to also take under consideration the minority opinion that you just think that the Indication and Usage Section needs to have additional information about what the limitations are of the use of this

product.

Am I getting that closer on that for us to consider, and when we come back to address the issue of if we don't recommend any stronger language, we want to leave it why we want to leave it and bring more information back to you about that.

DR. RAPPLEY: Can I ask then that the three who were not supportive of this motion give us a very concise statement about what further they would like to see?

DR. MURPHY: Yes, that would be helpful. Thank you.

DR. RAPPLEY: Okay. Dr. Kocis?

DR. KOCIS: I just feel we have enough information currently to prevent further deaths or further severe adverse events occurring before we change the labeling.

I feel whether it's contraindication or not, I don't feel, I don't know enough, as Dr. Daum says, I think professionals, experts need to do this, but you need to understand children are

given anesthesia by general adult anesthesiologists all the time, that pediatric anesthesiologists are not the only ones who provide that, and it's not clear to me, you know, all the circumstances.

Was this a pediatric anesthesiologist on your committee making the recommendation, were adult recommendations made, and what all that information was, but I think we've seen enough high-risk events that this neutral position to me is inadequate and yes, more information, yes, we'll get a better assessment of more adverse events and more catastrophic events, but I think we have enough information now to be stronger about our recommendations in the unintubated patient.

DR. RAPPLEY: Dr. Daum?

DR. DAUM: I have nothing to add. That's exactly my opinion.

DR. NOTTERMAN: Yes, I mean, I would echo Dr. Kocis's comment, that any time you have children going in for totally elective low-risk

surgery and have a severe complication when there is a very similar class drug available that's much lower -- that's lower risk and not express that sentiment in the labeling, I think that we're doing a disservice.

DR. RAPPLEY: Okay.

DR. MURPHY: That was very helpful.

DR. RAPPLEY: Thank you.

DR. MURPHY: Thank you.

DR. RAPPLEY: I also think we might internally, as we consider our process, think about when we are looking at medications that have a high-risk profile, whether they're used regularly or rarely or whatever.

Whenever we as a committee, not being the content experts in the particular discipline or of that particular medication, are reviewing high-risk meds, we probably need to allot more time for discussion and kind of walk through how the approval might have occurred in the first place.

Yes?

DR. SCHULTHEIS: I just want to make one comment, and it's important to bear in mind that these are not all totally elective low-risk patients, and the way the labeling was worded was intended to compel the anesthesiologists to make a thoughtful decision but not to tie their hands and compel them to follow a course of practice that non-anesthesiologists might find attractive.

DR. RAPPLEY: Okay. Thank you. Now, we are bumping up against lunch and our break, but we have an hour and 15 minutes to devote to celecoxib.

So, I'd like to suggest that we have our agency presentations first, we break for -- is that going to be workable? Okay. And then we will break for lunch and have sponsor presentation immediately after lunch.

Committee agreeable to that? Thank you to the sponsor for agreeing to that. Okay. So that would be Dr. Siegel up next. Thank you.

DR. SACHS: From the Department of Arthritis.

DR. PENA: Is Dr. Roca available?

DR. RAPPLEY: And I'll note this was a handout that should be at your table that was added this morning.

Celebrex (celecoxib)

Overview of Safety from Clinical Trials for JRA

DR. SIEGEL: Good morning. My name's Dr. Jeffrey Siegel. I'm with the Division of Anesthesia, Analgesia, and Rheumatology Products, and I'll be discussing celecoxib which was approved approximately a year ago for patients with juvenile rheumatoid arthritis.

Celecoxib, as you all know, is a COX-2 selective non-steroidal anti-inflammatory agent.

So, the purpose of my presentation is to give some background with respect to the considerations that were under advisement at the time of the review of celecoxib for approval for children with JRA.

As you all know, Celebrex was approved for use in children with JRA in December

of 2006. The efficacy was based on results of a randomized trial using a non-inferiority design comparing celecoxib at two doses to the active comparator naproxen.

The major issue at the advisory committee was potential safety concerns based on gastrointestinal and cardiovascular safety signals that were observed in adults, and I'm not planning to discuss efficacy at all, though if there are any questions, I can address them at the end. We will be discussing primarily safety.

So, the approval of celecoxib for children with JRA was based on efficacy and safety in Study 195. This study enrolled 242 children in the randomized portion of the study to receive either celecoxib 6 or 12 milligrams per kilogram per day or naproxen 15 milligrams per kilogram per day for three months.

202 children enrolled in a subsequent three-month open label phase to receive celecoxib 12 milligrams per kilogram per day for three months.

Safety in this study, at the 6 milligram per kilogram dose, showed the most common adverse events were gastrointestinal infections and infestations and nervous system disorders. Overall, the common adverse events were similar in type and frequency to those seen with naproxen.

In Study 195, the serious adverse events that were seen more frequently with celecoxib included GI disorders, primarily upper abdominal pain, pyrexia and musculoskeletal, connective tissue and bone disorders.

Overall, the serious adverse events and the severe adverse events seen in children receiving celecoxib represented events seen in this patient population and events known to be associated with other non-steroidal anti-inflammatory agents.

At the time of the initial review, we also looked at postmarketing reports for off-label use of celecoxib in children. Review of the postmarketing database gave no new safety signals