feasibility of even doing a multi-center study.

DR. BHAT: I can give you an example in my own unit. You know, we are seeing increasing numbers. We see about six to eight cases in a year, but of those, in the last four years we have used only in four cases so far.

So it is not that every baby that walks into the NICU will get this drug. If this effusion continues to accumulate and drain more than a significant amount of the fluid. Some call it as more than ten cc is considered as a significant accumulation.

The problem with that kind of a drainage is that not only it takes away the nutrition, but they lose a significant amount of protein. They also take away so much of lymphocytes, and really they develop lymphopenia and subsequent sepsis in a couple of reports already with that in the literature.

DR. RAKOWSKY: I guess the second question also. The second major use in neonates is for the triad of hyperinsulinism, chronic hypoglycemia and the nesidioblastosis. So the ratio of use of a treotide and that triad compared to chylothorax, is it about 50-50 for both or is it more for chylothorax?

DR. BHAT: You know, we have not used it for hypoglycemia. Most of the cases we have been able to maintain. This is a serious hypoglycemia I'm talking about with the hyperinsulinemia. Most of the cases we were able to maintain with the diazoxide these days. So very rarely we have used drugs like octreotide.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: My question was similar. It may be that we don't have this information, but I was wondering if you have a feel for the number of cases that might be available for study nationally in a year.

DR. BHAT: I think everybody is seeing an increasing number mainly because the prenatal diagnosis is so good nowadays, and the perineonatologists are very aggressive in managing these babies, not like before where they let them go and die in utero. Nowadays they are pretty aggressive, and they also know the neonatologists become so good in taking care of the tiny babies they are, you know, happy to deliver them in 30, 32 weeks after giving steroids.

So I think we are going to see more and more cases, but I can't give you an exact number.

DR. NOTTERMAN: Do you know if there's a registry.

DR. BHAT: I don't think so. I'm not aware of any registry. I think that's a good point actually.

CHAIRPERSON RAPPLEY: Dr. Goldstein.

DR. GOLDSTEIN: Two comments. One

is clearly if any study were going to be done they'd have to use the Vermont Oxford at the NIH Network.

But my other comment is regarding your observation that there are no PK trials. I just learned of a technology the other week, accelerated mass spec. that uses 50 microliters of serum and radiolabels carbon or another atom to do these PK trials, and you can use a population PK sample.

So it now actually becomes feasible. You know, previously blood volume issues got in the way with doing premature infants. That no longer is the case, and as a matter of fact, I saw preliminary data just last week from University of California at Davis on a Phase 1 PK trial in octreotide in premature infants.

DR. BHAT: I have not seen that.

DR. GOLDSTEIN: No, I'm the first human being to see it, but I think this accelerator mass spec. for the whole group

when we consider PK trials in preemies, infants, and small children is a potential suggestion or recommendation that can be made back to academic societies or industry.

CHAIRPERSON RAPPLEY: Dr. Rosenthal and then Dr. Motil.

DR. ROSENTHAL: Thank you very much, Dr. Bhat.

You know, I'm trying to get my arms around the idea of how pervasive is its use in the neonatal population. I'm wondering if you have any insight into whether guidelines for octreotide's use have made their way into the secondary literature, into the neonatology textbooks for this indication, or is it still not quite accepted in the field as a treatment for chylothorax?

DR. BHAT: I don't think many neonatologists really know. However, having said that, the perineonatology journal, most of the cases, these are all single case reports. They will come in the

perineonatology journal, and from I think two or three cases from Turkey and a couple of cases from this country, from Europe, from Hammersmith Hospital.

So actually I don't remember seeing it in textbook for chylothorax, but Sandostatin has been mentioned in the textbooks for hypoglycemia for other uses.

DR. ROSENTHAL: So, and again, I don't mean to push you. This may not be a fair question, but do you have a sense for how much it's being used in neonatology?

If you were to informally poll NICU docs, do you think most of them would say that they use it or would use it in this circumstance or is it something that only a very small proportion would use?

DR. BHAT: I think a very small proportion still. I would still prefer a conservative management trial for a short duration, less than a week, and if no response I'll try octreotide. I won't go this as a

first therapy for use in the neonates for chylothorax.

CHAIRPERSON RAPPLEY: Dr. Hudak, do you want to add to that?

DR. HUDAK: I guess I have a somewhat different impression because most of the neonatologists that I know are early adopters, and they tend to do things based on one or two case reports. So I think this is an agent that's fairly commonly used. I would think that probably most of these babies come -- the severe babies come to Level 3 units. Many of them come to university settings, and I think the people are quite aware of this therapy. Certainly in the post operative, you know, cardiovascular or even general thoracic surgery in the pediatric field it's used.

I'd probably say I'd guess probably 70 percent of the units would probably be using this. In terms of a number of babies a year, you know, if you go by the incidence of one in 1,000 --

DR. BHAT: One in 1,000, yes.

DR. HUDAK: -- then you're looking at 4,000 cases a year and probably 20 percent of those might come to a point where you'd consider using this before exhausting your conservative management.

DR. BHAT: Probably.

DR. HUDAK: So you're looking at, you know, 800 to 1,000 babies a year maybe as a guess.

DR. ROSENTHAL: And are you including both this hydropic situation as well as the post surgical situation?

DR. HUDAK: No. I think -- well, let me -- this is just the congenital chylothorax. If you look at the post-op hearts, you know, you're really looking at, you know, a pretty small number overall because heart disease is about one to two percent of the population, and those who develop, you know, chylothorax after a complete repair is a fraction of that.

DR. BHAT: Well, the highest number of uses after surgery or procedure, the highest incidence of post-op chylothorax and also after heart transplant. So actually if you look at the number of chylothorax treated versus the post-op chylothorax treated with the octreotide, there are more cases on the post-op side than on the neonatal chylothorax. But that may be because these are reported cases. Maybe they are using without any information, detailed information probably.

CHAIRPERSON RAPPLEY: Dr. D'Angio.

DR. D'ANGIO: I'm going to add to a highly scientific poll of neonatologists. One hundred percent of neonatologists in this room are aware of octreotide and its use, and I'd agree with Dr. Hudak that probably most people who practice in Level 3 university units are aware of its use and have used it occasionally.

I don't have anything to add about the likely number of infants to be -- well, I

do have a couple of things to add, but nothing as substantive as what Mark said.

First is that another group in which it might be used for the post ductus ligation children, chylothorax is relatively unlikely in that setting, but we've certainly seen it, and then the second piece of it that makes it difficult is that there may be as many as several hundred infants a year who could be studied, but they're going to be spread over a very large number of units, which makes it there's no one unit that's going to have a lot of experience.

If a unit that has one of the leaders that has used it four times in four years and we've used it three times in five years in our unit for the same indication, it's going to be very difficult to get a large cohort without enrolling a huge number of units.

CHAIRPERSON RAPPLEY: Dr. Motil, gastroenterology.

DR. MOTIL: Dr. Bhat, you alluded to the fact that you use octreotide as a last sort of choice on your medical management, but I wondered if you really had a protocol already in place that defined more precisely the time at which you would use it.

Do you wait X number of days with X amount of feeding, with a lymphopenia of X amount? I mean, do you have a defined protocol is what I'm asking.

DR. BHAT: Most of the cases I deal they are pre-term babies. If they are born hydropic we usually don't feed them. We do drain the fluid by chest tube for about seven days, and if the infusion continues to accumulate and drains, then we will consider using octreotide.

There are instances when I know from the literature they start very early, right after the admission to the NICU. We have not resorted to that kind of a therapy yet.

DR. MOTIL: So your major premise then is if they continue to reaccumulate in thorax.

DR. BHAT: A good number of them are just transient and they get absorbed very quickly. I had a case just recently with a Down's Syndrome with ascitis and a pleural effusion. They drained it before the delivery by putting a chest tube, and the ascitis was so mild I didn't have to do anything. It went away in a few days.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I just want to comment and make sure you agree with what I'm about to say, but certainly, you know, you outlined in detail the different etiologies acquired in congenital, and there are many models for the care of the newborn child, particularly the surgical child and particularly the cardiac surgical child, but in addition to some of the pediatric surgery there's overlap into where those children would be cared for.

Most of the programs that I have trained in the care of the newborn with congenital heart disease has gone to the pediatric ICU, not beside the NICU, and so I think that's not a universal but a fairly common model, and so there is a whole other population as you described up in the PICU.

While we are colleagues we also are separated by three floors in my hospital and I'm sure some distance in yours.

And there's also been a shift in the management of the newborn with general heart disease as we move further and further and younger and younger and more definitive, complete operations in the newborn, sometimes even the low birth weight child, and so certainly our unit has had a fairly significant amount of experience in dealing with the acquired forms of chylothorax, and we've seen it probably most commonly in post-op cardiac in the newborn. We've seen it on kids post ECHMO. We've seen it in some severe

lung disease, and then sepsis with profound thrombosis in lines and all of that. So we've seen it in a variety of diseases, and then at the other end, as you mentioned, kids with Fontan clearly, but the bidirectional Glenn.

So there's an apparent difference certainly in etiology and potentially to treatment and their response to treatment and to octreotide, and so we've actually probably gone the whole cycle without having a single randomized controlled trial in the sense that we had this problem. The problem was associated with significant mortality and is purely anecdotal data, and we began doing all of the standard care that you did, and added octreotide early on in our treatment plan.

We ended up early seeing that we weren't seeing a positive benefit from it. So we have already essentially abandoned that and moved on to definitive surgical intervention in most cases. It's not absolute.

So as far as there being a

guideline, a clinical trial, a consensus or anything, none of that has happened. It's purely been word of mouth, and we have a small group of people that get together a couple of times a year, and we talk about what we're having problems with and what we're trying and the like, and so, that was the statement part.

And then the question, and I would have saved this for you until later, but based on your paper, which certainly would be referenced in the critical care and likewise in the neonatal literature, have you had any thoughts on things sine this time as far as your view on utility, usefulness of octreotide, on the one hand, and, two, the risk complications and, you know, side effects, most importantly the severe ones that we're most interested in today?

DR. BHAT: Right. I agree with your comments and certainly there is side effects to this drug. We use this drug. It is only in the last four years we have started

using it, and we restrict it to the severe hydropic babies with their massive infusions requiring chest tube drainage, drains continuously for more than a week.

We have started using them with a pretty good success. All of the four cases have survived and they've gone home, and they didn't have any malformations, associated malformations in them, and I have not seen any necrotizing enterocolitis.

Is there a potential risk? It is definitely a potential risk by the mechanisms of this drug. Simply it decreases the blood supply. Put ischemia on top of it. If you feed them, it enhances the bacterial proliferation and subsequently developing necrotizing enterocolitis.

In our unit when these drugs are used, we don't usually feed these babies at that time.

CHAIRPERSON RAPPLEY: Dr. Hudak.

DR. HUDAK: I think, you know,

we're trying to sort of get our hands around a variety of experience here, which is not controlled by any means. I agree with you. I think that there is, especially in the large cardiac centers, there's a potential to do studies with a relatively small number, but you're really only looking at, I think, pretty much a single etiology, and that is an acquired post surgical event, and presumably the mechanism by which it works in that case is that it decreases the lymphatic flow long enough that the human process, whatever that is, occurs, and then you can stop the medicine and you're okay.

In babies who got, you know, congenital chylothorax, there are other etiologies presumably and the success in my experience anyway and by hearsay has been more variable, and I actually have seen a baby who developed NEC, you know, while on the medication.

So I think that, you know, there is

a load in the cardiac patients. Our surgeons have tended to use it, but they differed as to whether they believe that it works. So I think there's a healthy amount of skepticism out there that I think needs to be really studied carefully.

There's always the possibility that one man's interpretation is different than reality. Often this drug is started at a point where, you know, your drainage is decreasing. You start the medication and it continues to decrease, and it disappears. You say, "Oh, that's the drug."

Well, who knows? So I think in that case there's an opportunity.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: Just a quick question to the room. I feel like I have a sense for when it started after this indication of congenital chylothorax. How long are patients treated? What's their

overall exposure to it?

I remember seeing a slide that had 12 days on the X axis. Is that sort of a standard therapy?

DR. BHAT: The cases that I have reviewed, the shortest duration was about three days. The longest duration actually is more than a month people have given this drug, particularly some of the post surgical cases. They have given more than a month of infusion.

That is when I started really getting worried. Is it really beneficial? At what point will you really stop and think is the drug really making any benefit? I don't have that information

Certainly there is a varying duration, and a varying dose schedules, subcutaneous, IV boluses, IV continuous infusion, all kinds of dosing regimens.

DR. ROSENTHAL: Some other predictable side effects of the drug, like its

effects on growth hormone and those kinds of things, would probably come into play or may come into play if the duration of therapy is measured on the order of months.

DR. BHAT: Exactly. Good point, yes.

CHAIRPERSON RAPPLEY: Are there any other questions for Dr. Bhat before he leaves? Yes, Dr. Motil.

DR. MOTIL: One more question, Dr. Bhat. Would you say that in the congenital chylothoraces that all of these babies would be inclined to have prenatal steroids?

DR. BHAT: Up to the perinenatologist. If they know the etiology, it depends upon if it's a serious chromosomal anomaly. They may not give, but if it is simply a Down's Syndrome, for example, they diagnosed the serious chylothorax at 28 or 30 weeks of gestation, and it is progressing, and if they want to deliver that, I will definitely consider giving prenatal steroids

and interpartum steroids for two doses 24 hours apart. That is the standard, I think, that is recommended because the management after birth becomes really pretty effective for us in taking care of the babies on the ventilator.

DR. MOTIL: So in your experience for those babies in who octreotide was used, how those babies received antenatal steroids?

DR. BHAT: Yes, they did.

DR. MOTIL: Thank you.

CHAIRPERSON RAPPLEY: Any other questions for Dr. Bhat?

Okay. Thank you very much.

DR. BHAT: Thank you.

CHAIRPERSON RAPPLEY: Thank you for your presentation.

And Dr. Taylor? Is Dr. Taylor here?

DR. MURPHY: Now I'd like to have our division representative introduce herself.

CHAIRPERSON RAPPLEY: Oh, yes.

thank you, Dianne.

DR. LOWY: Hi. I'm Dr. Naomi Lowy. I am an adult endocrinologist, and I am a medical officer in the Division of Metabolism and Endocrinology Products.

DR. TAYLOR: Hello again. I will be providing a follow-up adverse event review of octreotide.

Octreotide, or Sandostatin injection and Sandostatin LAR Depot, is a somatostatin analogue. The injection formulation was originally approved in October 1988, and the LAR formulation was approved in November 1998. Pediatric exclusivity was granted in January 2006.

The adult indications are treatment of acromegaly in patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation and bromocriptine mesylate. Symptomatic treatment of patients with metastatic carcinoid tumors to suppress or inhibit severe

diarrhea and flushing episodes, and treatment of profuse, watery diarrhea associated with vasoactive intestinal peptide secreting tumors. There are no pediatric indications.

The pediatric exclusivity studies with the LAR formulation included a randomized double blind, placebo controlled, fixed dose, six-month study in 60 patients age six to 17 years, with hypothalamic obesity resulting from cranial insult in which efficacy was not demonstrated and a six-month open label extension study.

Safety results demonstrated a higher incidence of new cholelithiasis.

In April 2007, we presented pediatric adverse event reports received since marketing approval in 1988. There were 36 reports of serious adverse events, 25 non-fatal, and 11 deaths. From those reports we concluded that eight cases were possibly related to octreotide use; three reports of necrotizing enterocolitis, which is an

unlabeled event; one report of repeated episodes of hypoxia; and one report of repeated hypoxia with rechallenge, which is also an unlabeled event; one report of pancreatitis, which is labeled; and two reports of bradycardia, which is labeled.

The Pediatric Advisory Committee recommended that FDA should place information in labeling concerning the occurrence of adverse events in infants. Some noted at that time that information in the labeling should not imply that a causal link was established.

The PAC recommended that the FDA should consider ways to disseminate information to health care providers.

Also the FDA should consider improving consistency between Sandostatin LAR and injection labeling, such as including the negative exclusivity study results in the Sandostatin injection labeling, and that the FDA should provide a one-year update focused on observed post marketing adverse events of

necrotizing enterocolitis and hypoxia.

As requested, we searched the AERS database for reports received between February 2007 and May 2008. There were ten pediatric reports all serious, including one death.

Similar to the findings in 2007, half of all reports were in patients less than two years and primarily with the use of Sandostatin injection.

These are the reported off-label uses related to the reports. You see they are chylothorax, hypoglycemia, hyperinsulinism, insulinoma, pituitary adenoma gigantism, diarrhea, and in utero exposure.

There was one reported death from February 2007 to May 2008. The case involved a neonate born with multiple congenital anomalies, hypotonia and mild tachypnea. The patient was placed on Sandostatin injection for insulinoma two days after birth. The patient died one month later. The cause of death was not reported.

There was one case reported to FDA of necrotizing enterocolitis. This case involved a two month old with a history of prematurity, congenital heart disease and refractory chylothorax on multiple medications. The patient received three courses of octreotide. During one of the first two courses, the patient developed necrotizing enterocolitis. After two days on the third course of octreotide the patient developed bloody stools, bowel dysfunction, and necrotizing enterocolitis. The outcome of the patient is unknown.

There were no new reports of hypoxia. There were eight other adverse event reports which were hyperglycemia, hypoglycemia involving an in utero exposure, hypoglycemia involving a neonatal exposure, bradycardia and transient cardiac arrest, hypotension, fluid retention, and metabolic acidosis, osteonecrosis of the femoral head, and persistent infusion, which was considered a

loss of efficacy.

The Sandostatin LAR labeling was changed to remove the discussion of use of octreotide for congenital hyperinsulinism in March of 2008.

In summary, an additional ten reports of serious adverse events, including one report of necrotizing enterocolitis were received. One approach FDA is considering is to revise labeling to clarify that there are no approved pediatric indications and removed the description of the 49 published case reports from the Sandostatin injection labeling.

FDA will continue its standard ongoing safety monitoring for octreotide. Does the Advisory Committee concur with the above-stated approach?

And in closing I just would like to thank the people listed here for their help with this presentation.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Open for discussion. Dr. Rakowsky.

DR. RAKOWSKY: Thank you, Dr. Taylor.

This may be asking a lot, but is there any way to tease out from this information how many days the patients were on octreotide and if it was bolus versus continual infusions?

DR. TAYLOR: It depends on the report. Are you talking about the cases with necrotizing enterocolitis or are you looking --

DR. RAKOWSKY: Just in general, there's a trend. You have ten cases there.

DR. TAYLOR: Yes, I don't have that information.

DR. RAKOWSKY: Okay.

DR. TAYLOR: Not with me, but it is possible, depending on what's in the report.

DR. RAKOWSKY: So those reports may have been detailed enough to kind of tease

that information out?

DR. TAYLOR: Yes. I just don't have that with me right now.

DR. RAKOWSKY: Okay.

CHAIRPERSON RAPPLEY: Other questions?

I had a question on the table on Slide 8 where the cases are listed. Do I read this correctly that there were no U.S. cases reported in the last year?

DR. TAYLOR: Yes, that is correct.

CHAIRPERSON RAPPLEY: And then would you just remind me of why a decision was made to remove discussion of octreotide for congenital hyperinsulinism?

DR. TAYLOR: Well, I'll refer that to the division. You're talking about in the Sandostatin LAR?

CHAIRPERSON RAPPLEY: Yes.

DR. TAYLOR: Yes.

DR. LOWY: That decision was made since there is no indication for that use.

CHAIRPERSON RAPPLEY: So is that based on subsequent evidence or it was put there mistakenly? I just am trying to --

DR. LOWY: I believe, and if someone wants to correct me they can, but upon re-review it was understood that since there was no indication --

CHAIRPERSON RAPPLEY: It really was no evidence.

DR. LOWY: Yes.

DR. MURPHY: Remember I think we described it one time. We began this process before we had the legislation. There were some efforts if there was some information to try to get it into the label. A lot of controversy of whether that was a good or bad thing, and I think that when these products are coming up the divisions are using those opportunities to relook at some of that information.

CHAIRPERSON RAPPLEY: I just wanted to be clear that that decision was made as a

result of a review of most recent available data.

DR. TAYLOR: Yes, that's true.

CHAIRPERSON RAPPLEY: Other questions? Dr. Motil.

DR. MOTIL: In your review of the literature you comment on all of the off label uses for octreotide, and I'm puzzled by why you haven't seen or you did not report the use of octreotide for gastrointestinal bleeding as an off label use.

DR. TAYLOR: This is not from the literature. These are the off label uses that are associated with the AERS reports.

DR. MOTIL: Okay. So let me restate that then. In your review of the reports there were no instances where you had adverse events reported in association with the use of octreotide for GI bleeding; am I correct?

DR. TAYLOR: Yes. These are the uses of those ten cases that we had.

DR. MOTIL: So I guess I would only point out that octreotide certainly is used in children who have persistent, profound GI bleeding, and so I'm just reminding you that there seems to be at least one segment of the population which are not represented in this report, and ultimately the reason why I'm pointing that out is because of the comments that you're considering in terms of stating no pediatric indication. Because I think that then puts a hole in the armamentarium for setting perhaps where we look at portal gastropathies and profound bleeding for which we may not have accessible other modalities for significant bleeding.

CHAIRPERSON RAPPLEY: Could we hold the remaining questions and ask Dr. Gruber if he would step to the podium and give a presentation on behalf of the sponsor? And then we'll pick up questions from that point.

DR. GRUBER: Hi. I'm Dr. Todd Gruber from Novartis Pharmaceutical

Corporation. I am with the U.S. Drug Safety Group within the corporation.

The purpose of this presentation today is to share some of our global safety database data with the Committee and hopefully supplement some of the presentations that we've heard today.

The current Sandostatin U.S. package insert has the following indications in adults. I'm not going to read them. They've been presented already. The pharmacologic effects, as well, have been presented. It works on the endocrine system. It decreases splanchnic blood flow. It also decreases the release of certain gastrointestinal tracked hormones.

These are adult indications. We do not have any indication for use in the pediatric population, and our pediatric section, particularly the subcu. injectable label has information as was already discussed about hyperinsulinism, and we do agree with

the recommendation to remove as these are case reports, and there are no controlled studies in the pediatric population under age six.

Just a comment about some of the indications for the use of this drug outside of the U.S.. I would like to present this slide to put into context since I'll be sharing global safety data with the committee.

We have gastrinomas/Zollinger-Ellison Syndrome, insulinomas, refractory diarrhea, prevention complications following pancreatic surgery, and GI bleeding.

As part of our review for the Committee we performed a literature search, including MedLine and MBase, and we observed cases of use of the drug Sandostatin or octreotide in pediatric patients. We tried to look at the conditions that were being treated so we can get a sense of how off-label use was occurring with the drug. As you can see, a lot of the use correlates with the global indications for the drug.

Most of these are case reports. In fact, almost all of these are case reports. Many of them are favorable. Of course, we must acknowledge that many experiences if they are negative cases or negative experiences are usually not submitted or published in the literature.

So to make any risk-benefit decisions on individual case reports, of course, is difficult.

Okay. Now, let's shift our attention to the Novartis global safety database. It covers through the time of approval in the world, 1987, through the cutoff date that we used to prepare the report which we submitted this summer to the FDA. June 30th, 2008 was the cutoff data.

In our database we have 159 pediatric cases containing 549 adverse event terms. It looks like the gender distribution is fairly equal, and we have the age distribution presented on the table below.

Looking at the indications, and I will have a slide on that from the database. It appears that most of the patients under one year of age, the treatment indications were hyperinsulinism, as well as chylothorax. The older patients, 11 to 17 particularly, tended to be treated for a pituitary tumor, and a lot of the younger indications that we saw were kind of spread throughout all of the different age groups.

Okay. This slide is from data from the global database. We looked at the 159 cases, and we particularly wanted to go through and understand the indications where we had reports of adverse events. Again, this seems to correlate with the indications that we're seeing in the literature.

The next slide, and hopefully you can all see it. I tried to pack a lot into it. So I apologize.

What I did here is took the 549 adverse event MedDRA terms and we ranked them

by frequency, and I put the most common terms into this table. Cholelithiasis clearly is the lead term here at 22 reports. As you can see from these terms, a lot of the events that are observed in the reported cases, they are to be consistent with the underlying disease, and a majority and almost all of these terms are terms that are described in the label for the adult population.

Okay. Now I want to shift our attention. There were basically three areas that we were asked to present in our paper to the FDA and that are being discussed at this meeting. The first one is necrotizing enterocolitis. We start out with some general facts. I'm actually not going to read these except correct my parentheses with 25,000 babies. It's 2,500, as Dr. Bhat indicated, and he certainly did a very thorough job presenting this.

Just in red here we mention that term neonates who experience this tend to be

ill with other conditions: congenital heart disease, birth asphyxia, respiratory distress, abnormal fetal growth pattern, and metabolic abnormalities.

From the Novartis safety database we had five pediatric reports of NEC. As you'll see on the next slide, four of the five patients had an underlying congenital cardiac or vascular condition. The fifth case was a patient who had hypoxia with resuscitation within the first hour of life.

I apologize for the very detailed slide. I'm just going to try and highlight on some of the key aspects of this slide.

First I'll start with the age and gender column, the second column. If you can see the patients that experienced NEC were two months of age and younger. Indications basically were chylothorax and hyperinsulinemia for these patients, and I'd like you to focus in on the last column in red where I indicate the congenital abnormality or

vascular abnormality or in the fifty case the patient with apnea and resuscitation.

So, again, whether it was the underlying disease or if Sandostatin contributed on top of this disease, it's difficult to really make a determination. These are all very sick children and the use was probably as last ditch effort in many of these patients.

The second area or adverse event that we were asked to look at were cases of hypoxia. On this slide I'm actually going to focus on the second and third line first. These are two cases from a single case report. The same author had published two similar cases. These were both people who they were premature babies. They had bronchopulmonary dysplasia with pulmonary problems. Interestingly, these patients had necrotizing enterocolitis prior to being on Sandostatin, and these patients were on Sandostatin for other reasons, and they had pulmonary

hypertension and hypoxia.

The author of these case reports proposed a hypothesis that Sandostatin contributed to pulmonary hypertension which probably worsened the person's underlying pulmonary circulation and pulmonary condition leading to the experience hypoxia.

The top case is a 15 year old male who had ependymoma, gastric ulcer. This is a patient who had secretions after a GI procedure. So Sandostatin was given. Shortly thereafter, the patient experienced pneumonia with atelectasis, and the reporter in this case proposed a hypothesis that Sandostatin may have increased the bronchial secretions which set the milieu for the occurrence for pneumonia.

Okay. Lastly, I would like to present the pediatric cases where there was a fatal outcome. Again, this is coming from a Novartis global database over the last 21 years of reports to our database. In that

time frame we have 16 reports which were noted in patients with complex medical conditions. The age breakdown of the reports is below. One half of them are two years of age and younger.

A little bit messy slide, but it's an attempt to describe the causes of death to see if there's any trends and similarity for occurrences of the fatalities in these reports. Nine of the 16 cases the deaths were directly related to the person's underlying condition. The conditions are listed here. Several of these patients tend to be older patients with malignancies who died of progression of their malignancy. There was somebody with a liver transplant rejection who experienced complications from the rejection; another patient with graft versus host disease who had complications; a younger patient with hypertrophic cardiomyopathy and complications there; and then the last case was already presented under hypoxia. It was one of the

patients with hypoxia who was born prematurely and died.

The next group, if you see the brackets I have, we have four cases and then we have two cases. I'm actually going to skip down to two cases that have already been presented. Two of the necrotizing enterocolitis patients with congenital cardiovascular conditions experienced fatal outcome, and these cases were presented a couple of slides earlier.

Four of 16 patients also had congenital anomalies which were not necessarily direct cause of death, but they may have indirectly contributed to the fatalities, and again, some examples of these patients. There was a patient with short bowel syndrome who was premature, and they had liver and renal failure which the reporter felt was related to complications from the short bowel syndrome.

Another patient with aganglionosis

of the colon and obstruction and necrosis died of multi-organ failure and intracranial bleed.

Another patient who was premature with Noonan's Syndrome and congenital chylothorax, they experienced cardiac arrest and pneumothorax.

And then there was a case which I believe has already been presented on one of the prior slides where death cause was really unknown, and it's the patient with microencephaly retromicrognathia and hypertelorism.

Finally, the last case at the bottom, the patient was on Sandostatin for the indication was actually unknown in this patient. So whether they were treating a GI bleed or not is uncertain, but this patient died from a duodenal ulcer bleed. The patient was on prednisone, and they had nephrotic syndrome.

So in conclusion, Sandostatin injection or LAR is not indicated for the use

in the pediatric population. No formal clinical trials have been performed to evaluate the safety and effectiveness of Sandostatin in pediatric patients under the age of six.

There are multiple reports in the literature that have shown some benefit in the pediatric population. Of course, we all acknowledge the limitations of the literature and the fact that negative reports rarely get submitted or published.

Cases of serious adverse events, including the case of hypoxia, necrotizing enterocolitis and death, have been reported with octreotide use most notably in children under the age of two.

And lastly, the relationship of these serious adverse events to octreotide is not established as the majority of these pediatric patients had serious underlying co-morbid conditions, along with the use of concomitant medications.

I'd like to thank the Committee for giving me the opportunity to speak to you today.

CHAIRPERSON RAPPLEY: Thank you.

Questions? Dr. D'Angio.

DR. D'ANGIO: One question for you about your necrotizing enterocolitis cases.

DR. GRUBER: Yes.

DR. D'ANGIO: Do you have any information on the gestational ages of those infants?

DR. GRUBER: Well, the infants. I'm not sure I quite understand. As far as were they all carried to term or not?

DR. D'ANGIO: Yes, were they premature?

DR. GRUBER: I have no evidence. I would have listed this in my slide if these were premature.

DR. D'ANGIO: Okay.

DR. GRUBER: I say with a hint of uncertainty that I do not believe so.

DR. D'ANGIO: Thank you.

DR. GRUBER: I believe they were all term.

DR. BHAT: The two cases with the necrotizing enterocolitis that I know of, they are both term. One is reported from Hammersmith Hospital as a term baby. The quotational aorta had a lot of complications with the perforation of the heart from the catheter, various problems, and developed NEC.

The other one is also a term baby with nesidioblastosis, developed within two days NEC. Those are the two cases, but both survived.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I was just curious if you have any pediatric sales data, Sandostatin broken down at all.

DR. GRUBER: Yes, I do. It's a little bit difficult to interpret, but it will at least give a sense of some trends. We have Sandostatin injectable formulation and the LAR

formulation, and we can see that actually sales volume has decreased.

Again, realize this is Sandostatin branded. There is a lot of generic competition out there, and you know, our market has clearly decreased, but if the overall use of octreotide has decreased I can't comment on that.

We even tried to break it down by various models to see what age groups, and it looks like certainly the pediatric population is a very, very small amount of that.

We also looked by specialty as far as who seems to be writing prescriptions for this. It looks like hematology/oncology still leads. Again, how applicable it is to, for example, a newborn who is in the intensive care unit, this slide may or may not adequately meet the needs of the discussion.

Sandostatin LAR has relatively been stable. Again, pediatric use seems to be a very small amount of the use of this drug, and

specialty, again, hematology/oncology seem to be the leading prescribers of this medication.

CHAIRPERSON RAPPLEY: Other questions? Further discussion?

DR. MURPHY: I thank Dr. Gruber for presenting this information to the Committee.

CHAIRPERSON RAPPLEY: Yes.

DR. GRUBER: Thanks.

CHAIRPERSON RAPPLEY: I then have a question. I'm having a little bit of trouble focusing the question for the Committee. So I'm going to read to you how I think it has been presented, but you all chime in to revise this or you correct me.

So we're asked to consider revising the label, one, to indicate no pediatric indication for this medication; two, to add report of ten serious adverse events not previously reported; and, three, to remove the case reports which there seems to be some consensus that that needs to be done; is that correct.

DR. MURPHY: This is the beginning of the process that I was telling you about. If you'll look in your OSE review, you will see these recommendations, and so what we're trying to begin to do is give you some of the options or thinking that has been put forth.

So I didn't want to just repeat -- we didn't want to just repeat the whole thing. So it really relates to these are some of the recommendations that have been made. We, you know, might want to hear from the division if there's anything else that they want to say about this, but really we would like your input on what you think should be the approach to making this these labels.

Because, again, the SAR is what brought this product to the Committee, but the Committee made it pretty clear, I think, last time, and I think the division's thinking, too, is that these products ought to have their labels a little bit more compatible as far as the pediatric information in them.

But we want to hear your thinking about these suggestions, is really what we're asking.

CHAIRPERSON RAPPLEY: And did I capture those suggestions then accurately?

DR. MURPHY: Yes.

CHAIRPERSON RAPPLEY: Okay. Dr. Notterman.

DR. NOTTERMAN: So if I'm correct in understanding the recommendation, the first recommendation is to communicate to health professionals the receipt of these serious adverse effects. Is that correct?

I'm looking at page 774. And if I'm correct, then I just wondered in what form that communication would take. It mentions here perhaps a brief report.

DR. MURPHY: I'm just making sure we're on the most recent OSE review because there is a --

DR. NOTTERMAN: Okay. So maybe I'm looking at an older one?

DR. MURPHY: Yes. Which year review is that? Because I've got it tagged, too. I think it's the most current year. I'm just making sure.

It's the '07 review, yes. So go to page 714.

DR. NOTTERMAN: Okay, yes. It's basically the same.

DR. MURPHY: Just want to make sure.

DR. NOTTERMAN: Got you. Okay.

DR. MURPHY: The conclusions from the OSE review this year, you're right. One of them is communicate health care to the health care professionals.

DR. NOTTERMAN: And also number C is initiate an educational campaign targeted towards specialty areas.

DR. MURPHY: Right.

DR. NOTTERMAN: Yes. I would add to that pediatric cardiac surgery or pediatric cardiology.

CHAIRPERSON RAPPLEY: Dr. Goldstein.

DR. GOLDSTEIN: In addition to what Dan was saying, I think we have to be careful about this because these are as best as I can tell relatively unsubstantiated case reports and very sick children who have other potential explanations for these complications.

So I think it's perfectly fine to communicate to health care professionals that the FDA has received serious adverse events, including death associated with octreotide use in pediatrics, but there should be a caveat saying that this does not imply causality or whatever the appropriate statement is for that.

And then if that is acceptable, then in terms of the educational campaign I'm not sure how to educate somebody on a lack of education. There's no data really other than this happened. We don't know that it's

causal.

DR. MURPHY: And I think that's where the discussion ended last time, is that basically we have these events, but we don't have any way of determining because of the complexity of the cases and the patients that they're causally related.

DR. GOLDSTEIN: I can't see where it's going to be any different this time.

CHAIRPERSON RAPPLEY: Is it your experience that by sending out these communications people are more likely to report? Does spontaneous reporting go up?

DR. MURPHY: Not really.

CHAIRPERSON RAPPLEY: Okay.

DR. NOTTERMAN: Is there a mechanism or a process for consulting with colleagues, for example, in the Vermont Oxford Network or the Pediatric Pharmacology Network that's sponsored by the NICHD to hope to elicit a study or at least a systematic retrospective review?

Because I agree. I'm a little concerned about waving a very large red flag at our colleagues because, after all, there might be as yet unsupported and undocumented efficacy for some of these conditions, and we don't want to forestall the potential experience and potential benefit to children on the basis of disturbing reports in a very sick cohort of individuals with multi-system disease.

So I would like to try to do something to gather more data and more information in a systematic way.

DR. MURPHY: Prospectively.

DR. NOTTERMAN: Prospectively would be ideal, but in the absence of interest in a prospective study by folks, at least a systematic, population-based, retrospective collection might be appropriate through one of the networks.

CHAIRPERSON RAPPLEY: Dr. Hudak and then Dr. Rosenthal and Dr. Rakowsky.

DR. HUDAK: Yes, I'm just trying to think about what information is available out there. The last I looked at the Vermont Oxford and the NICHD databases, they do not capture this level of detailed information. So you would have to put that in as a new data field, if you will.

So I don't know if retrospectively we're going o be able to do anything wit the existing databases. The surgical database is different.

DR. NOTTERMAN: I'm sorry. Just so we don't lose track, there's also an organization called the Virtual PICU, which also I doubt very much if they capture this data now, but might be induced to, and that's out at UCLA, right? USC. Sorry. Out there.

CHAIRPERSON RAPPLEY: Dr. Rakowsky and then D'Angio.

DR. RAKOWSKY: Maybe before we get into a prospective study, just something as simple as surveying PICU/NICU and the

chronologists, just something as simple as a survey monkey just to see if you can actually comment in terms of how you use it, when you use it, and for how long and in what form, and then based on that sort of deciding how do we go forward with the study.

Without any data to kind of play with in terms of how to formulate a study, I'm not sure if it's fair to say let's start gathering this information. There have been a lot of attempts to kind of do things as simply as a survey to a big groups and just figure out in three or four questions can you tell us, and we usually get about a 40 percent response rate, which is a decent amount of data.

CHAIRPERSON RAPPLEY: Dr. Mathis did you want to answer that?

DR. MATHIS: Well, I don't think I can answer that specifically, but you had mentioned earlier today that National Institutes for Child Health and Human

Development and their work with Best Pharmaceuticals for Children Act, and they often have gone in and been able to do respective reviews to try and establish a path forward for some of these more difficult situations, especially in newborns where you do have very confounded situations.

So this may actually be a good opportunity to engage them.

CHAIRPERSON RAPPLEY: Because we could communicate to them that we thing this is an important issue to consider.

DR. MURPHY: It sounds like we're going to have to have a meeting with them. We've got quite a few recommendations.

CHAIRPERSON RAPPLEY: Dr. D'Angio.

DR. D'ANGIO: Just along the same lines of brainstorming, beyond a survey it might be reasonable. Vermont Oxford might be the best network because it's a little bit larger to see whether they would be willing to

add a question for a year or more onto their database about use of this, and that it might be possible in that case to gather enough data from enough people about what they're doing. It would be a prospective observational study rather than any sort of trial, but it might be another way to get at the data.

CHAIRPERSON RAPPLEY: Short of designing a study for you though, we could make a recommendation that we think the question needs to be explored further with appropriate databases and appropriate agencies.

DR. MURPHY: So the way this conversation started was about information, and it sounds like the Committee is saying we're not quite sure what that information would be, and we don't want to make a recommendation about an education when we don't really have enough data to help us.

So your recommendation at this time is that we pursue trying to find additional

avenues of information as to how the product is being used, what kind of adverse events people are seeing, and if they can give us any better information than we get from our normal adverse event reporting.

And then after that process and we have that data, we could consider whether we are any further along than we are right now. Is that what I'm hearing?

CHAIRPERSON RAPPLEY: Do people hear that, agree with that?

Okay. Dr. Hudak, then Dr. Rakowsky and then Dr. Kocis.

DR. HUDAK: Okay. I'd just like to, you know, emphasize the point that I think that, again, the use is fairly significant. I think, you know, the evidence for efficacy is lacking, and whatever means that we could use to work with the NIH to investigate this and find out once and for all with a discrete etiology whether it's effective would be very helpful rather than seeing this sort of be

pulled out at the last resort in every baby.

CHAIRPERSON RAPPLEY: Dr. Rakowsky.

DR. RAKOWSKY: I just want to add the caveat -- and I think Vermont Oxford does great work -- but I don't want us to just kind of box in on the neonatal groups because of sounds and leak space from Dr. Gruber's data. Seventy-five percent of adversity events were outside of the neonatal age group, and from what other people have been saying around the table is it's being used in all ages.

So we should ask other people besides just Vermont Oxford, but PICU, cardiology, et cetera, to make sure we capture as much as we can up front.

DR. D'ANGIO: When all you have is a hammer everything looks like a nail.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: Just comments for Dr. Murphy's thing and sort of putting a couple of things together.

So certainly gathering data

together is always a good thing, trying to get better data through NICU, PICU networks. Obviously planning trials are all wonderful, but time consuming.

I actually go back to Dr. Gruber's presentation, which I thought was fabulous and very well balanced, and more importantly, his conclusions from my standpoint were the same ones that he reached were the ones that I reach.

I think I have the biggest problem with this drug is simply the label, as you have identified, the need for changing the label, and I think if it were to reflect Dr. Gruber's conclusions, which overlap with mine, and it sounds like many of the people here, that would go a long way in sort of just making the pediatric world aware of the fact that there are serious complications clearly cannot be attributed to the drug, but they are there with the disease in patients who are having the drug.

And likewise, to remove sort of that sense of, well, here's 49 studies that are showing efficacy, and I would say none of them showed efficacy. They're purely all case reports, not that we can ignore that, but that needs to grow into some randomized trial to look at efficacy. In a way, we can assume efficacy just because we're seeing these reports, as numerous as they may be, and I think the final thing is clearly where there seems to be efficacy in congenital chylothorax, and that seems to be one of the first places to want to start and to get out there and get safety and efficacy data all together.

So my only point was I don't want to see another period of waiting before and acting on the things that we talked about.

Thank you.

DR. MURPHY: One part of that is in a little bit of conflict with the other, what they recommended, which is the part that's not

in conflict is that you're saying that you agree with the fact that we need to revise the label to clarify that there's no pediatric indications and that we need to remove the description of the 49 published cases.

And so I guess maybe, Marsha, it might be helpful to just have us take that and see how many members agree with that, and then we can come back to the other -- is there any other statement. Because Keith has proposed another statement to go in the label, and how much -- how unanimous the Committee is or is not on that statement.

CHAIRPERSON RAPPLEY: Okay. I heard five different issues raised: one, some consensus about removing the case reports.

So do we have agreement that those case reports -- so that's our recommendation.

DR. MURPHY: So we have consensus.

CHAIRPERSON RAPPLEY: We have consensus.

DR. D'ANGIO: Could I add one

thing? And I know we're biasing things in favor of -- in the direction of safety and away from anything have to do with efficacy, but some of the information that's in the label right now with those case reports does have to do with adverse events, and I'm not sure we want to lose that part of it.

CHAIRPERSON RAPPLEY: Well, that would be then there's a part about -- that's another point that we will talk about adding ten new adverse events.

DR. D'ANGIO: Well, there are adverse events in those 49 cases. I don't know how the agency would want to rework things to take out the implication that this is an efficacious drug while leaving the similarly biased but perhaps important information about what the side effects were.

CHAIRPERSON RAPPLEY: So I guess a question is when we had the presentation about ten serious adverse events, was there a review of those case reports when that list was

compiled?

DR. MURPHY: Well, you know, you guys don't have to give a specific wording on the adverse events. You can tell us we think you need to put some additional information in the pediatric labeling about adverse events that are being reported.

You know, when you put in the statement, or if you out in the statement about this product is not indicated the following. You know, it doesn't have to be just that wording from those cases or the ten. So you can be more general is that I'm trying to say.

CHAIRPERSON RAPPLEY: Okay. Dr. Hudak, did you want to say something about the case reports, about removing the case reports?

No. So there is consensus about that.

DR. MURPHY: Okay. So we've got consensus to take out the 49 case reports.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: Okay.

CHAIRPERSON RAPPLEY: Now, then the next issue is addressing all serious adverse events that have been discovered on your review and including those in the label.

DR. MURPHY: What is the Committee's recommendation for including the adverse events that have been reported.

CHAIRPERSON RAPPLEY: I think the Committee is recommending that we include those adverse events that have been reported.

DR. NOTTERMAN: I was just going to say that I think they should be included, but I don't know if everyone necessarily needs to be included. So I would just phrase it by saying that we recommend that the division review the adverse reports and include those that seem appropriate and substantive.

DR. MURPHY: Okay, and I heard some concern that we make it clear that we have a determined causality. Is that something the Committee is in agreement that that statement

be in there?

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: I think at least for me there's a little bit of confusion. Most of the labels that we look at when we describe adverse reactions, they're based on clinical trials. We have these rates, those rates, compared to placebo, whatever it is.

In this case what we're saying is, okay, we don't have the clinical trials on these. So we don't want to imply efficacy that is not there, but we sort of don't want to lose the safety information that we did glean from the 49 plus ten, and that's I think at the level we are. The rest is a little bit up to the agency how in the world to accomplish that.

DR. MURPHY: Yes, and there is a post marketing section for adverse events, post marketing, and we can make it clearer that these are pediatric adverse events that are being reported in that post marketing.

I mean, it's up to the division, but I'm just saying for your information, you're right. Normally when we're describing it, it's the trials, but there is in the label a place to put the post marketing adverse events, and it's a matter of clarifying that these are pediatric even though there's no indication, and I'm sure that you all can find a way to write that, though it's not indicated, he following adverse events have been reported for children, though no causality can be determined, something like that.

Because we've seen that in some of the other labels.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I just want to be consistent with process and what we've been doing with all of our drugs and certainly what we've been advocating.

So first from the one clinical trial that we -- I don't even think we read it

this time but last time we did, which was in the obesity. So we do have adverse events. They are just like we would from trials, and we would include that just like any other drug in any study.

DR. MURPHY: Yes, it's in there.

DR. KOCIS: And in particular, note the gall bladder disease, which was greater in the kids.

But then, two, in the same way we look at data one year later from post exclusivity. You run your safety thing which gleans from errors and gleans case reports, which presumably when you looked at that this time or the time before you found those same 47 case reports unless they're brand new, reviewed them in a way, removed duplicates and all that sort of thing, and then presented to us, you know, what you found as death, serious, and other things.

And so those findings and the process that we go through all the time I

would recommend that we follow, and the only point to that is to not all of a sudden grab every side effect you can read in any of these case reports that are unprocessed and the like and include that in the adverse events section.

CHAIRPERSON RAPPLEY: And then the fourth area was about education, a suggestion that an educational campaign be undertaken and the suggestion from some members of the Committee is that it's premature to undertake an educational campaign. Is there agreement with that?

PARTICIPANTS: Yes.

CHAIRPERSON RAPPLEY: Okay. So we think it's premature at this point in time to undertake an educational campaign for health professionals.

DR. MURPHY: I guess that was just the question that Ann was bringing up, that there were two parts to that recommendation. One was education and one was communication to

health care professionals. So we just need your feedback separately on it.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I guess I wouldn't know what it would fall under, which category, but in what way would we notify health care providers specific in pediatrics in the areas subspecialists would likely use as that. There is a new label. Once that process is complete and the new label is derived to communicate that, because I think that that's, again, personally what I have the most trouble with where we are right now in acquiring knowledge and what's out there and available to practitioners who are making decisions about whether to use this and what to be concerned about that.

So in some way -- and, again, I don't know what the normal process is -- I would not favor sort of just changing the label and then waiting for people to try to figure that out. In some way we can alert

that there has been a new label change for this drug, and it provides all of the things we've talked about so that everyone is aware of that and what we've talked about.

CHAIRPERSON RAPPLEY: So communicating that there's a label change, but not undertaking an educational campaign. Does that answer your --

DR. MURPHY: Until we get further information, yes.

CHAIRPERSON RAPPLEY: Then there was one remaining issue, but --

DR. MURPHY: Yes. Let me just -- we've been struggling with how to communicate the labeling changes. That's one of the issues, is that -- and it's not just for this. It's really a bigger issue. It's the issue of how do we make pediatricians aware of the constant flow of new changes that are occurring to the labels.

We have them up on our Web, but having been in practice, I can tell you you

don't just go down and cruise your website on the FDA to see what new pediatric label changes have happened.

So, you know, how do we do that? It doesn't rise to the level -- I'm not the expert in the agency on this -- to putting out a health care advisor. It's not that level, and I think we could get with some of our people internally in Communications and see if they have any other ideas because the agency is trying to be more communicative.

Susan, is she still here? Yes, Susan, do you want to? Do you have any thoughts on this you'd like to add?

And before she says that, I just wanted to let everybody know that one of the other things that we've done is we've worked with the American Academy of Pediatrics now on their newsletter. You may not read your journals, you often read your newsletters. So this is the newspaper that comes out from the American Academy of Pediatrics every month.

It now has a set FDA update in it, a section, 200 words only.

So we can -- you know, we've been putting information in the suicidality and the anti-epileptics was in there. This upcoming article will talk about the upcoming LABA meeting so that pediatricians will be aware. We're trying to alert them, even get ahead of the curve if you will, to upcoming changes.

And we can consider that as one of the things we can do, but again, it's the editors of the AAP who end up making a final decision on that. So just before Susan contributes here, that is one way we can alert pediatricians to different label changes, in addition to doing a little summary that we do also through the academy.

DR. FARRAR: And again as the academy rep. or someone who represents, I think that would be something that would probably be something that could be worked out if the FDA was interested in using that.

DR. MURPHY: We do it every month.

DR. FARRAR: But I mean for this.

DR. MURPHY: For this, yes. We will come to you if they reject us.

DR. ROSENTHAL: And, again, we're talking about the publication as AAP News. Is that what you're talking about?

DR. MURPHY: Yes.

DR. CUMMINS: I'm Susan Cummins. I'm the senior science advisor to the Pediatric and Maternal Health staff, and I'm a pediatrician and an epidemiologist, just so you know who I am.

The Med Watch Program has two components. There's a component that manages the AERS reporting of adverse events to the agency. It also has a communication component. It has a listserv with over 110,000 members on it, and you can sign up on the listserv if you're interested in getting MedWatch reports. It automatically distributes new safety information to anyone

on the listserv.

It also does a monthly safety labeling update. So it compiles on a monthly basis any new labeling changes to certain sections of the label, contraindications, warnings, precautions, adverse events sections, and compiles those and distributes it through the listserv.

So that's another way that any safety labeling change that's made is routinely distributed to people who sign up, and it's posted and available on the FDA website.

CHAIRPERSON RAPPLEY: Thank you. Then that leaves us with one remaining aspect, the question posed, and that is do we support revising the label to state that there is no pediatric indication.

So I'll read to you since we don't have the slide available. The FDA is considering this approach, revised label to clarify there are no approved pediatric

indications.

And in doing those things that we just described, as well as revising the label to indicate no pediatric indications. The FDA would continue standard ongoing safety monitoring for octreotide.

Does the Committee support this statement? Further discussion? Dr. Notterman.

DR. NOTTERMAN: Well, I thought the tenor of the discussion earlier, not with respect to the label changes, was that we don't support routine monitoring, but in fact we think that the agency should be aggressive in trying to accomplish or receive new data, prospective as possible or at least systematic and population based if retrospective.

So I don't think -- at least I don't agree that it should be routine monitoring from this point forward.

CHAIRPERSON RAPPLEY: I think I heard Dr. Mathis say that there's no mechanism

to access additional databases, that we would have to make that recommendation to the Best Pharmaceuticals for Children Act.

DR. MATHIS: We actually very actively worked with NICHD on having drugs prioritized on the priority drug list and also worked with them on the best approaches to get it studied, and they have a lot of resources for doing things like retrospective reviews or thorough literature reviews.

So they would probably be a really good resource for us to be able to get both retrospective and prospective data on this particular product. So that wouldn't be part of an FDA safety monitoring task. It would be a project that we would work with NICHD/NIH on.

CHAIRPERSON RAPPLEY: So should we give you a formal recommendation that we think you should do that?

DR. MURPHY: If that's what you want us to do, which we thought is what you

were telling us to do.

CHAIRPERSON RAPPLEY: Yes, okay.

DR. MURPHY: I mean, you hadn't gone back to catch it, but it looks like you're there now, that you want to make that formal recommendation, and I guess what Dr. Notterman is saying is that -- I'm trying to figure out -- what he's saying is that instead of never coming back to us again, having FDA not come back to you again, that part of that is that it's really not the routine answer because you want us to come back if and when we get this or at least give you an update as to where we are with that process of trying to get this additional information.

CHAIRPERSON RAPPLEY: So we would request a follow-up for octreotide.

DR. NOTTERMAN: Follow-up based on your consultation with whatever appropriate colleagues you think you need to talk to at NICHD or elsewhere.

DR. MURPHY: Okay. But we never

finished the discussion about the no pediatric indication.

CHAIRPERSON RAPPLEY: Well, I thought that we did include that.

DR. MURPHY: Okay. I just bifurcated that discussion.

CHAIRPERSON RAPPLEY: I thought that the Committee -- well, we didn't take a vote. So Dr. Rosenthal.

DR. ROSENTHAL: So regarding this issue of putting in the label that there are no approved pediatric indications, can somebody help me understand why we're asking that question with this drug and we weren't really willing to ask that question with Ambien this morning? Isn't it a similar circumstance where we don't have efficacy data and we do have some risk data?

The statement that we weren't willing to actually make a statement to this effect for that drug, but for this one we are, or someone help me understand what I'm missing

in my postprandial state.

DR. MURPHY: I'm also going to try to remember the conversation, but I think the issue with Ambien was that even though --

DR. ROSENTHAL: Yes, but there was a controlled trial that showed lack of efficacy in a specific population and showed what seemed like a real increase in the risk associated with those who received the active agent.

DR. MURPHY: The discussion there was can we go in and then put in a specific statement that in that population you shouldn't be using it. I thought that's what the discussion was this morning, and that was the difference.

CHAIRPERSON RAPPLEY: Dr. Pena has reminded me that we probably shouldn't revisit our discussion because we don't have the staff here that provided that information for us.

DR. MURPHY: But I do think there is a difference in what the circumstances were

is all I'm trying to say. But you're asking what can we do for this.

The issue here is does the Committee think that the present label for this product states clearly enough or is sufficient to make the practitioner understand that this product is not indicated for pediatric use for any indication.

DR. HUDAK: I think the answer to that question is no, and I think that's why I think it needs to say explicitly there is no approved indication of pediatrics for this product.

I think with Ambien -- that doesn't exclude a practitioner from using it by any means. With Ambien I think it was an issue of if you put in the label don't use it in children with ADHD, that would be language that would be interpreted by people not to use it in children. We didn't want to close that off for non-ADHD children.

CHAIRPERSON RAPPLEY: Okay. I

think the question --

DR. MURPHY: -- specific indication is one thing.

CHAIRPERSON RAPPLEY: But I think also we need to make a decision on this product based on the information given to us about this product, and if in fact we wish we had done something differently, we can talk about that -- with another medication -- we can do that at a different time or an appropriate time.

Dr. Mathis.

DR. MATHIS: I'm sorry. Can I just please make one final point for the Committee to consider when they're making this consideration? And that is that the indications that are in the octreotide labeling currently do not have age restrictions. So if you go back in and say this has no pediatric indication, you are changing the indication. You're restricting the indication if you go in there and say

that.

Because right now there are no age brackets within the stated indications. I think that's what Dr. Rosenthal was getting at.

So in some ways if you do go in and say there aren't any pediatric indications, you are changing. I mean, I think that there are ways to work around that, but I am just saying that if you go in and say there are no pediatric indications you are removing a pediatric indication for three indications that are currently in the label depending on how you look at it.

I'll stop there before the lawyers get me.

DR. MURPHY: That would be difficult. I mean, right now we had this discussion about where we don't have age brackets, but other places in here it says adults under those indications. It does say adults, that it has been studied in adults.

So I think Lisa is trying to point out one possible -- how shall we say? I don't want to say hole that the people might have -- but clearly, in FDA-speak, this product is not indicated for children right now. That has no indication for it.

DR. GOLDSTEIN: Is it not indicated or is it that efficacy and safety has not been established in the pediatric population?

DR. MURPHY: It has no indications for pediatrics.

DR. GOLDSTEIN: But what if you have a VIP element and you're 17 years old? Wouldn't you want to be able to treat your patient with that? I would.

DR. MURPHY: Yes.

DR. NOTTERMAN: With this I mean.

DR. MURPHY: Yes, yes, and you could. You could.

DR. NOTTERMAN: Well, I would prefer to see the expression safety and efficacy in the pediatric age group have not

been demonstrated, which is a more passive statement than to face the statement that there is no indication because I don't see a relative difference between treating VIP in a 17 year old and treating it in a 19 year old.

DR. MURPHY: And that's, you know, what's up for discussion. That's what we want to hear about. That's why I've brought us back to that.

DR. NOTTERMAN: Right. No, I understand.

DR. MURPHY: But that is the recommendation or one of the recommendations that we have. So if you agree with it or you don't agree with it, we need to hear that.

CHAIRPERSON RAPPLEY: Dr. D'Angio.

DR. D'ANGIO: And if there ever were a situation in which there is no evidence in pediatrics, there's no evidence in pediatrics and that's probably what we should say. I mean, we've had two hours of no evidence. So that's probably a very

reasonable thing to say, is that whatever the boilerplate was that we were bashing on the last one that we were talking about sounds perfect for this one.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: I want to go back to something that Dr. Mathis said, that once you begin saying no, you're putting the pediatrician or neonatologist or whoever it is in a somewhat more difficult situation.

Right now I think we all agree that we don't know. That's why we're not willing to go on an education campaign, et cetera, et cetera. If so, then adding more language might actually be less, and I think that Dr. Rosenthal is right. When we looked at Ambien, we had a conclusion about ADHD, and we refrained from adding any other language having to do with anything else because we don't know.

And I think we're in the same situation here.

CHAIRPERSON RAPPLEY: You would agree with using the more passive statement, the traditional statement.

DR. CNAAN: Either the more passive statement or let it be all together and not tie the hands of neonatologists trying to do last ditch efforts, trying to do something.

DR. GOLDSTEIN: I would just point out that we actually have lots of evidence, but we have evidence for use, not for efficacy. We also have some safety evidence as well.

The issue with Ambien is that we had a lot more of use, but still no efficacy. So I think it's a similar situation, and Dan's statement that, you know, efficacy and safety haven't been established I would concur with.

DR. D'ANGIO: And I'll agree.

DR. GOLDSTEIN: Because the use is not going to go away.

DR. D'ANGIO: And I'll agree. What

we don't have is the evidence to make any stronger statement than safety and efficacy not determined.

CHAIRPERSON RAPPLEY: Okay. Then I am going to revise our recommendation to the Committee. We did not vote on that one previously. We engaged in this discussion, but based on the discussion, then we would recommend to the Committee that they consider using the traditional statement about safety and efficacy in children have not been demonstrated for this product, and that they continue the ongoing monitoring of safety, but give us a follow-up.

Those in support of that statement?

And those opposed.

So there is consensus on that statement.

DR. MURPHY: Thank you.

CHAIRPERSON RAPPLEY: Thank you.

So that concludes then our discussion of our products, and we move now

into a presentation for our ethics discussion. Dr. Skip Nelson is a pediatric ethicist in the Office of Pediatric Therapeutics.

DR. NELSON: So I'm going to walk you through 62 slides in less than 45 minutes. So hang on since I know I'm the only one between you and your ride home.

What I'd like to do is give you a report on a meeting we had in June and remind you that the charter of the Pediatric Advisory Committee includes a number of aspects around ethics.

First of all, there is an Ethics Subcommittee which is chartered to do reviews under referrals of 21 CFR 50.54, and there will be a review on December 9th that FR notice published last Friday. Four of you are going to be involved in that review, and then all of you or not all of you, but those you can make it on Tuesday afternoon, December 9th, will then opine on that, and that will be a recommendation, not a protocol, that

involves the use of GCSF for stimulation of stem cell transplantation given to healthy sibling donors and how that should be approached.

In June --

CHAIRPERSON RAPPLEY: Excuse me. Can I just interrupt you for a minute, Skip?

DR. NELSON: Sure.

CHAIRPERSON RAPPLEY: So the charge to the Committee today in receiving your information is at the end we concur with --

DR. NELSON: You listen.

CHAIRPERSON RAPPLEY: We listen and we either concur or we don't concur to that --

DR. NELSON: Actually there's no votes. There was no votes at the meeting. So it's more informational.

CHAIRPERSON RAPPLEY: Okay. Thank you.

DR. NELSON: There is no question at the end, no quiz.

So what I'd like to do is go

through the agenda and basically at the meeting in June we discussed the prospect of direct benefit, which is a particular category under Subpart D, and we did this using specific cases. And I'm going to run through both edited versions of the slides, as well as some of the cases, to give you a feel for the questions that were discussed, and you'll see these cases as we run through.

The structure of each discussion in using the hypothetical cases was to present some background concepts, present the hypothetical case, and then some discussion questions, and again, the slides I'm presenting are edited for this presentation. Everything that I'm presenting to you is up on the website for the June 9th and 10th meeting of the Ethics Subcommittee. Of course, these slides are up for today's meeting.

So first background presentation, and you'll see this concept. When I think about the special protections, I start with

scientific necessity. I then move to appropriate balance of risk and benefit, and those are the two categories that I think are most important, and then we talk about parental permission and child assent.

Scientific necessity as I've stated it should be the children should not be enrolled in a clinical investigation unless it's absolutely necessary to answer an important scientific question about the health and welfare of children.

Now, study design, sample size and the like. The interesting thing is extrapolation is a practical application of that and I'll get into that in a moment.

Now, this notion of scientific necessity is actually tied to equitable selection. If you look back at the discussion by the National Commission in the 1970s in establishing the general IRB criteria, instead of talking about gender equity and ethnicity as equitable selection, in pediatrics they

were talking about enrolling subjects who were capable of informed consent first, before children, and not enrolling children unless it was essential.

So that's what equitable selection means under the general IRB criteria when applied to pediatrics, and that's not the way we often think about it.

So extrapolation, you've heard about this. This is the formal definition in the legislation. This is taken from the Pediatric Research Equity Act in FDAAA where the course of the disease and the effects of the drug are sufficiently similar to be able to extrapolate.

You've also seen this. Lisa put this up for you yesterday, this flow chart, if you will, about how extrapolation can be approached.

I think the point I want to make here is extrapolation in my mind is an important ethical principle which is

scientifically complex in its application. So it's not to say that you should extrapolate as a presumption, but it's an important principle to then focus on and ask can you do it in this circumstance. What's the data in support of it? What's the evidence in support of it, et cetera? Not that extrapolation is something that one should do.

Now, when you look at appropriate balance of risk and benefit, very briefly, in the adult regulations, which is that first bullet point, you can balance the risks against anticipated benefits to the subjects, if any, and the knowledge. So for those philosophers in the audience, if you took the, if any, and the, and, the bottom line is you can expose adults to significant risk in the pursuit of knowledge. You can't do that with kids.

With kids, if there's no prospect of direct benefit, the risk is restricted, and if there is prospect of direct benefit, the

justification of those risks is restricted, and that category 50.52 is the one that we talked about specifically at this meeting, and here is the actual language. I won't read it, but only point out the A, B, and C at the bottom where it talks about the risk being justified by the anticipated benefit, which is one component of that balancing, and then the relationship of this benefit and risk has to be comparable to available alternatives.

So it gets into a discussion of whether it's to be in the trial versus out of the trial. The National Commission's language for this was that no child should be disadvantaged to be enrolled in a clinical trial, and that was the particular category that we focused on during the meeting.

Now, as I said, we did three hypothetical cases. The first case which generated some attention was a hypothetical case of enrolling adolescents in an HIV vaccine clinical study.

I might add I wrote this case before the Merck STEP trial came out. It was discussed afterwards, which is why it generated some interest, and I might say that all of these were, in fact, hypothetical cases, and I'm not going to go through all of the details. I kept the slides on the cases so that you had the sense of the depth, if you will, of the case description. My own view is that you can't do ethics without cases, and to have rather thin description of cases you end up just making up the facts, and then everyone is talking about different facts instead of about the different ethics about the same facts.

So the purpose of the cases was to try and develop some rich descriptions that could stimulate discussion. So this first one was basically a proof of concept trial for adults, which involved a specific approach to HIV vaccines, which was not the one included in the Merck trial. It had sufficient

preclinical testing to make it a suitable candidate and in non-clinical animal models suggested efficacy.

Some early phased trials suggested T-cell response. One of the issues within HIV vaccines is, in fact, there's no immunological correlates of protection, which is obvious since there has been no evidence of protection to date, but doing this kind of work is difficult; that the side effects were not severe, and that, in fact, it was a fairly standard approach as far as the early phase, adult human experience.

And the endpoints was reduction of HIV infection and reduced viral load. And then standard conduct in terms of access to antiretrovirals and the like, and in the interest of time I'm not going to read that slide.

Now, the question is fairly complex, and the purpose here, as you can see, was to get people to think about what it means

to decide to enroll an adolescent in an adult trial or at what point in the adult trial. So the question was when would you decide to enroll adolescents in the above Phase 2 clinical investigation.

We also asked as part of the discussion addressing the threshold of evidence necessary to establish that the study intervention offers a sufficient prospect of direct benefit to justify the risks of vaccine administration. In other words, that's the requirement under 50.52.

So, for example, would you require interim or final results from either a Phase 2 or 3 study? How does the lack of an immunological surrogate impact on that judgment? If you had a surrogate, you could perhaps use that to try and establish direct benefit.

Issues that the subcommittee was asked to consider included the distinction between evidence sufficient to establish the

prospect of direct benefit versus evidence sufficient to establish efficacy. The point there is fairly simple. If you require efficacy evidence in order to do research establishing a prospect of direct benefit, that's a circular problem. You can never then do the study because you need the study results before you can actually start it. So obviously prospect of direct benefit is different than efficacy.

The choice of adolescent populations of those that are at risk, and then the use of immunogenicity or safety data to bridge from adult to adolescent populations. So this was the range of issues that the Committee was asked to discuss and to give you a sense of the Committee's discussion, these are taken from the Flash minutes. So this is already up on the Web around this Committee meeting and doesn't reflect, if you will, my interpretation of what was said.

But they basically identified a number of factors. First of all, the importance of scientific necessity; then talked about age; behavioral considerations; physiologic differences; at risk, clinical target populations, relative efficacy. And so basically you can see it was a fairly rich discussion of how one would go about targeting, if you will, a particular adolescent population for this particular research.

The Committee also talked about scientific necessity and extrapolation, the prospect of direct benefit and the like, and what it would mean to qualify direct benefit, and recognize the importance of studies in children when scientifically appropriate.

This isn't by way of conclusion. The purpose if I might add to this meeting was to have a sort of diverse discussion with the goal of trying to inform what I would hope to be the writing of guidance on the application

of Subpart D, which at this point there's no pen to paper as of yet, since I haven't gotten to it.

So the second case we approached was choice of control group, one of my favorite topics. I happen to think ICH-E10 choice of control group is one of the more important ethical documents as a guidance document from the International Conference on Harmonization.

Now, of course, the selection of an appropriate control group is critical to the design of a trial. It allows you to discriminate patient outcomes caused by test treatments and by other factors. It's essential in the inference of causality in a clinical trial. E10 talks about different types of control groups where you can have concurrent controls or non-concurrent or external controls, and the one we focused on was a placebo control, but this lists the other types of controls that are feasible

within that concurrent control approach.

Now, ICH-E10 goes on to say that as a general rule research subjects in the control group should receive an established effective intervention, but there may be circumstances where a placebo or no treatment control would be, in fact, appropriate.

The criteria by which that document suggests that there is no established effective intervention -- that's fairly straightforward -- when withholding it would result in at most temporary discomfort or delay in relief of symptoms, allergic rhinitis, for example, might be an example of that, or when use of an established effective intervention as a comparator would not yield scientifically reliable results.

You know, this, for example, trying to do a non-inferiority margin trial where you had no previously established data to say what that non-inferiority margin ought to be, or you're not able to establish that under a new

trial condition the drug you want to use as a comparator may, in fact, work under those new trial conditions, and the use of placebo would not add any risk of serious or irreversible harm.

Now, that points out that you could have a circumstance where withholding standard treatment would result in serious or irreversible harm even when you can't do an active controlled trial. And ICH-E10 even points out that under those circumstances that may be a trial you cannot, in fact, perform.

The other aspect of this is component analysis. So what this says is you need to tease apart a protocol into those aspects that offer direct benefit and those that don't and evaluate the risks of each component separately. So that's component analysis.

And the question on the table, for example, is does the placebo offer a prospect of direct benefit, yes or no? And then how

would you evaluate the risks of being in a placebo group in the particular trial that we looked at.

I'm just going to skip over that one.

So the example that we used was a hypothetical case description of a study of inhaled corticosteroids in children with mild persistent asthma. Now, although this was a hypothetical case, it's actually designed following the guidance document on the evaluation of growth effects of inhaled corticosteroids.

And this was the presumption, is that a new inhaled corticosteroid presumably would have decreased steroid induced effect on bone growth, which could really only be established if you had an appropriate placebo control to be able to show that you didn't have that effect, which is one of the reasons why the choice was to look at mild persistent asthma where the potential withholding of

inhaled corticosteroids would not necessarily impact severely on that child's health care.

So this was the proposed clinical trial design which was a fairly standard one-year randomized, double blind, double dummy, parallel group, placebo controlled study in kids between five and eight years of age, which is the time of maximum growth.

And here because of the issue of assay sensitivity not only was there a placebo arm, but also an approved inhaled corticosteroid with known effects on linear growth as a positive control. Because if you knew that that didn't have any effects on growth within that trial, then you would not assume a negative result for the other investigational agent that was, in fact, interpretable.

Notice how much trial design is involved in ethics.

Randomization, of course, is fairly standard, to one of four groups, and then

subject selection criteria, FEV of less than 80 percent, but selected to have mild persistent asthma, the point there being a population to where the risk if you will of withholding inhaled corticosteroids was a debatable point, but certainly didn't rise to the level of a serious concern about harm.

Concurrent medications were permitted. Leukotriene inhibitors, for example, although this was prior to some of the suicidality signals and Monte Lucast, so that might be taken into effect. One could decide, for example, to use chromolyn if you wanted to avoid that particular side effect.

And then there would be rescue therapy with beta agonists as needed throughout the study, but certainly not a long acting beta agonist pending your discussion in December.

Primary endpoints, obviously linear growth philosophy, and then an efficacy endpoint as well. There was some discussion

of the treatment of acute asthma exacerbations. That would be treated according to standard therapy, and then there was a withdrawal criteria which in this case was considered, I think, four rescue treatments with oral corticosteroids, and then they would be converted to open label rescue therapy.

So let me give you a flavor of the questions. Question 1, please discuss the assessment of the potential benefits of this clinical investigation for the enrolled children.

So part of the agenda here is what does it mean to say someone has a direct benefit. Can you say that it's a direct benefit to just be in a clinical study? Can you say the placebo group directly benefits or not, and how does that affect on your analysis, if you will, of the acceptability of the trial.

So in other words, do the potential

benefits apply equal to the intervention and control groups? Can you say placebo benefits people?

The distinction between benefits that may occur as a direct result of the experimental intervention versus those that may occur from inclusion in the clinical trial. There was much discussion that kids are better off in a clinical trial, and should that be considered a direct benefit was one point of discussion.

And then whether any additional monitoring procedures required by the administration of the experimental product would be considered a direct benefit or evaluated as a risk, since if you don't get the experimental mentioned and don't need that monitoring, is that best considered a risk or a benefit under that category?

Question 2 then, after thinking about benefit looked at issues of risk. What's the risk of withholding the known

effect of inhaled corticosteroid from the two experimental arms and the negative placebo controlled arm? What's the impact of the selection of subject population on those risks, in other words, mild or persistent, moderate asthma, how would that impact on your assessment of risks?

And then the role of other study modifications that were in there, such as the use of rescue medications, control of medications and the like.

And then Question 3, once you have the benefit and risk side is to put it all together and take a look at how one would evaluate this clinical trial. One of the issues in evaluating benefit of the trial, do you unpack it into the individual arms within the trial and look at risk-benefit within those arms or do you just sort of consider what happens to a child before randomization into those arms and then issues, again, to consider would be the direct benefit for each

arm and the efficacy as the primary object.

So you can see this was a fairly complex analysis, and I might say I don't think many IRBs go through this complex level of analysis, but frankly, editorial comment, they should.

So the Subcommittee discussion talked about the prospect of direct benefit. Again, this tells you some of the issues that they covered. The discussion was a fairly rich, not necessarily consensus of the different issues.

Commented about the benefit to the child and the risks of the intervention. Basically thought each treatment arm was important. By and large the Subcommittee felt you needed to evaluate it according to the treatment arm and not by the whole study.

Discussed the various aspects of trial design. Discussed some about compensation and how that one evaluates benefit. Talked about a notion of equipoise,

standard of care, pre and post randomization analysis.

I think having read through this, a fairly rich discussion that I think is quite informative for moving forward and advising people how to evaluate these sorts of trials.

So once we talked about that, on the third day we tackled another issue which is of interest to me, which is in a situation where you don't have adult trials or any adult data, how can you establish the prospect of direct benefit from animal studies.

Now, here's the fairly standard model, if you will, the pediatric drug development. You had some preclinical animal models. You go into a healthy human adult to do some Phase 1 dosing. You then get adults with the disease, do some safety and efficacy, and then once you've moved it far enough along you find children with the disease, and then you move forward.

Part of the difficulty is sometimes

you've got a product that you shouldn't give to a healthy human adult, occasionally, and sometimes there is, in fact, no adults with the disease to be able to go from health human adults to children with the disease. And then, in fact, sometimes going from non-clinical, in fact, to children with the disease is the only option.

And the point here about healthy children is no. Healthy children are not to be enrolled in any FDA regulated clinical trial. That would be a longer discussion, but I'll just put that out there.

So the question is how do you do first in children. In other words, if the risk of this intervention has to be justified by anticipated benefit how do you establish a sufficient prospect of direct benefit in a situation when you've got a fairly risky intervention, when the only option you've got is to do some preclinical animal testing to some extent?

So here's some thought about prospect of direct benefit. First of all, what does it mean to say it's direct? Well, it means it's mine and not yours, first of all. Benefit is my benefit, not your benefit.

The notion there is that it results from the research intervention, not from something else that might happen. In other words, if you say giving me this drug is a direct benefit, it's the giving me of the drug that's the direct benefit, not from other interventions, including the protocol.

This is referred to often as the fallacy of the package deal. If you throw in enough health care into a research protocol, you can make it a good thing to be in it, but that's not meant to offset the risks of the experimental intervention, and the word benefit is often preceded by clinical to indicate that direct benefit relates to health status.

Now, the other thing is it's

related on the structure of the intervention. Dose, duration, method of administration, and not on the investigators' intent. Those intensivists in the crowd might recognize the doctrine of double effect here. If I give 20 milligrams per kilogram to a narcotic naive subject and claim my intent was to relieve their pain, I hope you would tell me that that's not my intent. Clearly what I chose to do did not reflect my intent.

So intention is related to the action, not related to one's psychological state of mind. Unfortunately, post Descartes we think intent is just in the mind. Intent is not in the mind. It's a function of the action itself. But we unfortunately have the modern mind-body dualism that we have to contend with.

There needs to be some empirical evidence. Now, what level of evidence is an open discussion, but the justification of risk by possibility of direct benefit can be fairly

complex, similar to a clinical judgment about the appropriateness of that risk exposure within a clinical setting. The importance of direct benefit to the subject, the possibility of avoiding greater harm from the disease, the risks of the experimental intervention, as I said, can justify expected from that same intervention, and the justification of that is set in the context of disease severity.

Degree of disability, life threatening, availability of alternative treatments? So once you get past does this provide a prospect of direct benefit, then you have a whole set of justifications around the nature of that benefit.

And in thinking about this, one proposal that I and Sara Goldkind, who is also within FDA working as an ethicist within the Good Clinical Practice Program, came up with what we call a sort of sliding threshold, that in fact the animal data necessary to establish a sufficient justification for the prospect of

direct benefit varies with the severity of the disease and the adequacy of alternative treatments.

Structure would be generally insufficient, but you could have functional changes based on a mechanism of action, molecular targets, biomarkers, physiologic pathways or taking a human target, throwing it at a mouse and proving you can hit it in terms of transgenic technology.

You could get if you have the appropriate animal model a clinical disease model using either a surrogate endpoint or a clinical endpoint. No one raised the question about the approval on the PK data of Levaquin for inhilational anthrax. Well, behind that is the fact that in fact there is no human data for the approval of any of the fluoroquinolones for inhalational anthrax. That was based on the animal role for ciprofloxacin, if I get that correct, Dianne.

So here you had an efficacy

approval now with dosing for children based on an animal rule with no human data because obviously it's unethical to do inhalational anthrax studies. So that point kind of flew by, but I didn't bring it up at the time.

Dosing, of course, is an issue because if you simply pick a low dose, it may not be the most effective dose. So looking at toxicity within animal studies and starting low, you also have to pick a dose that has the potential for offering some benefit, and not necessarily just move into a clinical study with the lowest dose.

So the case that I chose for this was a clinical trial of human neurostem cells for neonatal hypoxic-ischemic injury, again, a hypothetical case of which there's some literature and some development in the area. Neonatologists are obviously familiar with hypoxic-ischemic injury. The neurological deficits it results in learning disabilities, cerebral palsy, or mental retardation, and the

thought is that injury to the oligodendrocyte precursor cells contribute to this pathogenesis by disrupting the maturation of myelin forming oligodendrocytes, and the hope is if you could replace this maybe you would be able to have some impact.

There's some preclinical experience in different neonatal mouse models that these could, in fact, work. You could get them where you need them to go, and they can do the things that you want them to do, and the study hypothesis was that you could insert human neurostem cells, may reduce or reverse the neurological deficit secondary to neonatal brain injury.

There are a number of potential animal models which I won't go through which are perinatal rodent models, pre-term fetal sheep, non-human primate models, and basically the question was how does one go from these models to a first in child-human trial.

So these were the questions that

the Subcommittee was asked to discuss. Please discuss the ethical issues in selecting an appropriate subject population for the initial clinical development plan of these products. Issues you may want to consider include differences in the natural history of the disease between adults and pediatric subjects which may influence the timing of the cell insertion there. The question would be, in fact, is there an adult equivalent or not, and if not, how does one go about that.

Whether dosing safety and/or efficacy should first be established in suitable adult subjects prior to enrolling children; differences between pediatric and adult subjects with hypoxic-ischemic brain injury, meaning the possibility of direct benefit; the usefulness of the safety information; the assessment of physiologic response and long-term effects.

In other words, explore is there any possibility of doing adult studies to get

this into kids. This was a fairly wide ranging hypothetical discussion of that issue.

And then, of course, once you've approached that issue, then what about the ethical issues in designing a first in children clinical trial? How would you establish a sufficient prospect of direct benefit? What are the range of animal models available? And then the different types of physiologic changes in response to the experimental product; what kind of evidence would you demand to say that there's a prospect of direct benefit?

Getting there and just showing that they myelinate? Getting there that they myelinate and show some change in function, or would you expect some clinical change that the mouse model can get up and walk in some way?

And then how would you frame this in terms of the severity of the disease and the availability of other discussions?

And, again, the Committee

discussion was fairly wide ranging. These, again, are from the Flash minutes. One of the discussions was the purpose of the study and the target outcomes, in other words, the ability to measure physiologic and clinical outcomes as important ethical considerations when designing a study and determining the appropriate subject population.

Again, the definition and assessment of direct benefit was discussed, the use of surrogate markers, the pros and cons of younger versus older subjects, the various regulatory approaches for the appropriate review of a pediatric clinical investigation, the use of compassionate use and innovative therapy models, limits of animal studies, and use of adult models as proof of concept prior to pediatric studies.

So all of that was part of the discussion. So in summary, in June we had a fairly rich discussion of the application of this category, greater than minimal risk but

presenting the prospect of direct benefit to FDA regulated research using three hypothetical case examples, and this discussion will inform future FDA guidance on the application of 21 CFR 50, Subpart D, to FDA regulated clinical investigations involving children.

So that is a whirlwind summary of what Amy and Elaine and Geoff lived through, and as I said, December 9th there will be an Ethics Subcommittee meeting followed by a full Committee meeting to discuss this protocol that was referred under 50.54, and I think those same three plus Melissa have agreed to participate in that discussion.

So I'm happy to answer any questions. My time is yours.

CHAIRPERSON RAPPLEY: Would you put that last slide up that had your summary? I think that might be helpful.

Any comments or questions from the group?

DR. NELSON: Last slide. Okay.

CHAIRPERSON RAPPLEY: Yes, Dr. Goldstein.

DR. GOLDSTEIN: Skip, that was a wonderful presentation. Did your group also have a discussion on that last case about the issue that you brought up with the prior case, which is selection of control group specifically oftentimes when children were left with problems about establishing a gold standard in terms of measuring outcome? In this particular case, to be a gold standard in terms of measuring injury severity?

DR. NELSON: We did not carry the discussion of choice of control group, as I recall. I mean, I haven't read through the transcript in detail, but I don't recall much discussion of control groups on the third case.

But you're right. In many of these diseases how one infers the efficacy of the product, particularly if it's an uncontrolled

case series is difficult. It can be easy if, in fact, the endpoint is mortality, but if the endpoint is a variable morbidity, that would be difficult.

But you know, that is an issue, but the group didn't discuss it much on that third case.

DR. RAKOWSKY: Skip, are you going to have transcripts available for us to tap into?

DR. NELSON: The transcripts are available on the Website for the meeting which was June 9th and 10th. So if you go to, in fact, the Pediatric Advisory Committee Website, you'll see the Ethics Subcommittee listed there, and the transcripts are already posted.

DR. ROSENTHAL: I'd just like to take a moment to thank you and congratulate you for pulling off what was really a fantastic discussion. I thought you assembled just some brilliant participants, and the

discussion was both relevant and erudite, and my compliments to you for doing that.

DR. NELSON: Thanks, Geoff, and I'll pay you later.

CHAIRPERSON RAPPLEY: Other questions or comments?

Thank you, Skip. We accept your report.

DR. MURPHY: And he really doesn't mean to scare you all. I mean that. The subcommittee will, of course, explore all of this in great detail, and those of you who are participating on it, and they will bring a recommendation and you'll have an opportunity to ask question and have discussion, but there's a subcommittee of ethicists for a reason. You can tell this is a very complex field, but I actually think it's a terrific opportunity for the full Committee to hear the thinking that is going on at that subcommittee.

So I hope that you were as

enthusiastic as we are about the development of this.

CHAIRPERSON RAPPLEY: So thank you all.

I think a couple follow-up things is I'll be e-mailing you about some ideas that you've generated about how we might process the abbreviated reviews and so we'll discuss that on e-mail.

And then I will talk with Carlos and Dianne and Lisa about the best way for us to communicate to the Best Pharmaceuticals for Children Act, especially around our concerns around the atypical anti-psychotics.

And I'll follow up then with you in drafting what that communication might be so you can help on that.

DR. MURPHY: I think that's a really interesting way for us to try to move some of these areas forward. I mean, these are mechanisms that you have provided to us, but we really haven't used that as completely

and as thoroughly as we could.

So I think it's a very interesting suggestion for whoever, for your recommendation.

CHAIRPERSON RAPPLEY: And isn't it in the spirit of agencies talking with one another, which we have been all asked to do?

DR. MURPHY: Yes.

CHAIRPERSON RAPPLEY: So thanks, everybody, for coming out today, and we'll see some of you again in December and certainly in March.

DR. MURPHY: I was going to say thank you all very much. We will see you again in December.

(Whereupon, the above-entitled matter concluded at 4:03 p.m.)