I mean, if I were confronted with that data on a baby, I wouldn't know what to do with it. I go by bradycardias and desaturations and prolonged apnea that's, you know, greater than ten to 15 --

DR. JAMES: So the pneumogram is not a useful tool for you?

DR. HUDAK: I don't find the pneumogram useful.

CHAIRPERSON CHESNEY: Dr. Blackmon.

DR. BLACKMON: Well, there are some standards, to just speak to the issue of the pneumogram. There are some standards that require not only the monitoring of respiratory effort in air flow, but also heart rate in making the diagnosis of obstructive apnea.

And I think whether that's the kind of apnea that you want to get into or whether you want to use the chime study extreme event documentation, which was, I think, probably a better standard for an apneic or an episode of instability that's concerning.

I'd like to go back to Dr. Hassall's comment or question about indications for doing

fundiplication. I've worked with probably a dozen or more pediatric surgeons over the course of my time. A specific weight criteria was not usually an issue.

The indications for fundiplication surgery on a respiratory basis were clear documentation of failure of clinical improvement in a time when it should have occurred, usually manifested by recurrent aspiration episodes clinically ore recurrent appearance of infiltrates on X-ray that were in association with changes in the feeding pattern, usually increasing in volume feeds or bolus feeding.

Rarely did I ever have an infant that had fundiplication under two kilos in the absence of profound neurologic damage. Thus, those infants that were really profoundly damaged, and there was no way to advance enteral feeds without some mechanism of feeding in the stomach, did we ever go under two and a half kilos.

But the issue of when we went to fundiplication really was severe respiratory complications, by and large, in the absence of either esophageal abnormalities of an anatomical and

functional nature or severe neurologic impairment.

DR. HUDAK: But that's your one to two babies a year.

DR. BLACKMON: That's correct.

CHAIRPERSON CHESNEY: Dr. Spielberg, and then I'd like to ask Dr. Murphy and Dr. Raczkowski where we go next.

Dr. Spielberg.

DR. SPIELBERG: I'm confused, which is not unusual with neonatal studies. I mean, we were involved in a study of a very different compound where we couldn't get two neonatologists in the same unit who attended month to month to agree how to feed the babies the same way.

I disagree that this is an easy study. I think this is a profoundly difficult study to do because I don't know what we're treating yet, and I don't really know the patient population and targets that we're looking at.

I've heard a lot about different kinds of babes with different kind of physiology, different maturational states. Working against us are two

things: one, entry criteria and, second, duration of time because things are changing.

Apnea rates are changing with age, as are rates of GI function changing with age. So we have an outcome variable changing at the same time we have an input variable changing, all at the same time.

This is why in a sense I would be driven towards an enrichment design. Simply saying, you know, what is clinical practice right now like, in honesty, you try the drug. If you think it works, you keep the babe on the drug. If you think it doesn't work, you take the babe off the drug.

You know, a good clinician paying close attention to the patient by whatever criteria is going to behave that way. In a sense what this design does is say if we're going to do the study, we enter patients. Those who respond, we see if that response is really due to the drug in question by doing a withdrawal phase.

Having said that, I think the studies are going to be confounded by definition because of changes in maturation, changes in disease state,

influence of the drug, that indeed we're working with irreversible inhibitors here, which is why the PK doesn't match the PD.

It's going to be a very, very difficult to assess study, which to me says I'm not sure yet that the study is ready for prime time. That is not to say we don't want to do it, and it's not to say that it's not important to get this information for the situation that Dr. Gorman described, you know, the happy spitters, where in honesty that's a practice issue.

You know, my second son, you know, was, again, an enormous laundry problem. He hasn't vomited in the past 14 years, but for that first nine months we used more detergent than was available in the City of Toronto to deal with the issue, but he grew and he was fine. So it didn't matter.

And I had a pact with the pediatrician not to intervene until nine months, and eight months, 30 days, and boom, it stopped.

We don't want drugs used that way, but doing studies is not regulating practice, and in a

sense our common sense in practice guidelines should reflect that we shouldn't be using drugs as first choice for diseases that aren't diseases in the first place.

So that's not the issue. So I'm still concerned we're not quite there in terms of design. If I was responsible for designing the study based on everything I've heard today, I still don't know how I would do it, and I really wouldn't have confidence that I would answer the question, which is: do these drugs work in some children with apnea and bradycardia effectively?

And if I can't convince myself I can design that and really get the definitive answer, I'm not sure yet I should be doing it without some additional data, perhaps a good NIH study to provide the rationale and better definitions of the patient populations or better tools that we can use to make sure once we do the definitive study that it gives us a definitive answer.

CHAIRPERSON CHESNEY: Thank you very much.

You speak very eloquently for many of us

who are still very much in a quandary, and when I think about my general pediatric attending, what are the patients where I really want an answer? It's those ones where we have tried everything and it still isn't working. Sometimes they came in with a life threatening event. Sometimes they are failures to thrive. Sometimes they are just repeated apnea and bradycardia.

And when we get to the point that our only alternative is reflux surgery, I would love to be able to look at PPIs in that population because of your experience. I think that's phenomenal if we could modify our surgical rate as dramatically as you said, even given that maybe it's not a very long lasting effect, but then maybe that's even more reason to see if these drugs work.

So, you know, when all is said and done, I can't really speak for the neonatologists, although I understand that population because we see some of them that aren't in the ICU.

But thank you. I think you really expressed the difficulty we're all having with this.

Dr. Hudak?

DR. HUDAK: I'd just like to make one comment, and that is that we deal with this all the time. The babies are changing maturationally in every organ system, and yet we've done good clinical trials in neonatology with objective results, clear endpoints, and so forth.

And I will still insist that this study can be done and be meaningful and be interpretable and give us an answer, not every answer, and it will probably spark more questions if we show efficacy, as to exactly what population that the drug is effective in and how can we better identify that population.

But I think as a first study, this can be done. If I took your reasoning to its extreme we wouldn't be able to do any study of any agent on any organ system, you know, because of all of the factors that you mentioned.

DR. SPIELBERG: Absolutely, but I think my greater fear is that we'll end up with a negative study that will perhaps end up disadvantaging kids who would, indeed, benefit from the drugs.

And we're dealing with a situation here where labeling does have an impact on that and where studies do have an impact.

I'm just saying we've got to work towards a study design that optimizes the chance of showing something if it is there, and I'm just not sure we're quite there yet with the endpoint as opposed to cardiovascular endpoints or other things which we --

CHAIRPERSON CHESNEY: Dr. Wilfond and then Dr. O'Fallon.

DR. WILFOND: This is a question for Dr. Spielberg.

You know, it sounds like what I hear you saying is that studies are needed, but you're making the distinction between the study that was done through this written request process versus through some other non-FDA related approaches.

And I'm not sure I understand the distinction between those two about when you pick one approach versus the other. So that's really sort of an open question for anybody, I guess.

DR. SPIELBERG: Well, just from an

industry perspective, in terms of designing a trial, when we're doing a good clinical practice design trial with endpoints that, in fact, have been validated and tools that have been validated either by us or by external investigators, we have reasonable confidence that we're going to be able to present data to the agency that the review division is going to be able to look at, make sense of, and that everybody is going to be happy with.

There are many diseases for which we just don't understand enough yet how to evaluate that process. We're trying to do a study that has all of those implications for labeling and such. It would result in data that are really uninterpretable.

And those are often very hard judgment situations in pediatrics because now the beauty of what's happened in the last five years is that lots of drugs are being studied. The difficulty is that in the age before when so few drugs were being properly evaluated, you didn't have to worry about validated endpoints because there was nothing to study.

Now we truly have to worry about validated

endpoints in order to do those studies, to get away from anecdotal medicine into evidence based medicine.

And the sad part is not only in this field, but in many other fields of pediatrics, we've been struggling because, in fact, when we look for those endpoints, they just aren't there, and it could take two, three, four years to get the endpoints so that we can actually do the study.

CHAIRPERSON CHESNEY: Dr. O'Fallon.

DR. O'FALLON: There are a number of things that concern me. One of them is that I think what I'm hearing is that there really haven't been studies done to get the information in this population. So patients are being treated within almost the lack of any information.

Any kind of information would be valuable, I think. So there is a philosophy of clinical trials, you know, the large, simple trial, but basically the idea is you enter the patient if the doc feels that the patient needs to be treated and wants to treat him.

You know, this would be done. We'd work i

tout, but it seems to me that, you know, you could define if the doctor feels that the patient needs to be treated with this sort of thing. Then enter them in. The treatment would be given, and there would be the well defined failure escape criteria because, you know, if it's clearly not working, they don't have to go eight weeks.

But then there would be the randomization at eight weeks or six weeks or four weeks or whatever you guys thought would be the appropriate thing, and you could see whether it was the drug that was doing it or whether it was just something else.

But you would have a lot of information at the end. So if you found out that the ones that were always cured were, you know, the ones that turned six months or seven months or something during the course of the trial, you'd have some evidence that maybe it was maturation that was underlying and not the drug.

I think that doing a study like this would at least give useful information even if it wouldn't identify the best drug for any given condition.

CHAIRPERSON CHESNEY: Dr. Nelson.

DR. NELSON: I think we've sort of come full circle to the question as to whether or not any of these pulmonary manifestations or breathing manifestations, apnea, bradycardia, are pH related. And I was writing down four different study design choices, and we bounced back and forth between the assumptions about the role of pH.

So, for example, if it's an add-on to prove an effective therapy in nonresponders, you're excluding pH related disease, except for Bob's caveat about those who might not respond to renitidine. If you do it as a replacement for proven effective treatment and then a randomized withdrawal, you're assuming pH related disease.

If you do a standardized placebo controlled trial in nonresponders, you're assuming non-pH related disease.

And then if you bounce back to an active control equivalence trial, renitidine versus a PPI for apnea and bradycardia, you're assuming a pH related disease.

So it strikes me that until we sort out

whether we think apnea and bradycardia are related to the gastric pH, it's not clear to me we have a study design that would make sense of those four choices.

CHAIRPERSON CHESNEY: Dr. Hassall.

DR. HASSALL: Yeah. I think that by suggesting, Dr. O'Fallon, that you should do these studies because there's information to be had you're a priori assuming that it is an acid related disorder. because we're using acid suppressing drugs.

I mean, I have a paper in front of me from Pediatrics, January 2002, "Gastroesophageal Reflux," just as an example of one piece of literature, and apnea of prematurity, no temporal relationship. Here they didn't even use pH studies or acid was not even a consideration. They used impedance, in other words, looking for bolus reflux.

So I think we're getting back to the question: is it the obligation of a study like this to prove cause and effect, or should we first know what causes it in order to even embark on a study in the first place?

CHAIRPERSON CHESNEY: Dr. Ebert?

DR. EBERT: Well, just briefly in response to Dr. Nelson, my other question would be whether it would be possible to do a three arm trial, one where you would have a placebo as well as an H_2 blocker as compared to agents for the PPI. So that might address in some ways the issues that you talked about with regards to whether, in fact, this is an acid related disease.

DR. NELSON: Well, having the placebo arm in there would help you know if it's an acid related disease, but the presumption is if you believe it is an acid related disease, then having the placebo arm in there would be considered unethical.

So the honest answer is I don't know. I'd have to look at the evidence and decide. It's unclear to me. Is there any evidence that suggests that neonatal apnea, bradycardia if there is reflux is related to acid at all?

CHAIRPERSON CHESNEY: We don't have an immediate response. Let me turn to the FDA folk and provide us with some guidance.

DR. RACZKOWSKI: Okay. Well, I think

we've had a good discussion on the Question 2. I don't think we're going to get to -- I'm sorry -- Question 3.

I don't think we're going to be able to get to Question 4. Unfortunately our clinical pharmacologist, Laura James, left because she had a flight to catch, but I wondered if anyone happened to have comments, including from the audience, about the pharmacokinetic and pharmacodynamic studies.

We did hear at the break from both Dr. Gardener and Dr. Kerns, and I'd be interested in pursuing Question No. 5 just very briefly.

Let me just say that the approach that the FDA took in children greater than a year of age is that enough is known about these acid related diseases in that age group that if you have a blood level of the proton pump inhibitor and you can match that in a child to the blood level in adults, that children and adults are not that dissimilar that you could anticipate that you would have similar pharmacodynamic effects in kids.

Part of it was a feasibility issue, that

it's difficult to do pharmacodynamic studies in kids more than a year of age, and just in terms of doing a sample size.

But the underlying assumption now was that if you have blood levels, sure, there's no immediate correlation between PK and PD, and sure, we know that it takes time for these drugs to build up their pharmacodynamic effects, but if you can match exposure in an adult and in a child, then you would anticipate a similar pharmacodynamic effect in kids more than a year.

Kids less than a year, we were unsure, and so we asked for pharmacodynamic data.

CHAIRPERSON CHESNEY: Could I ask Dr. Kauffman? I'd be interested in his comments and then maybe Dr. Kerns would also be able to comment on this number five, specific PK/PD issues.

DR. KAUFFMAN: I think this is a PK/PD relationship that is different than what we most times deal with where we have a fairly direct relationship between what we're seeing in the plasma and what's happening in the effect chronologically.

This is an irreversible inhibitor, I guess. It's an irreversible inhibitor. So the effect last over a different time frame than what we see the compound's life in the plasma or measuring it.

What we would like to be doing is measuring it at the receptor, but next best is measuring the effect that we can measure in terms of acid production or acid concentration or hydrogen ion concentration in the stomach.

It seemed to me with this relationship that one approach would be to look, as Victor said, to look at exposure whether you define that as area under the curve in the plasma. that's probably the easiest way to do it. Look at exposure and try to approximate exposure in the child to what you have evidence for in the adult; that that measurement of exposure results in this 24-hour suppression of acid, and extrapolate that information, assuming it has essentially the same effect.

If we weren't completely comfortable with that, we could do a small group of children where we actually measure acid concentration over time and

corroborate that our assumption is approximately correct.

And then we may want to do that -- I think the value of that is we're probably going to find that the -- and there was some hint of that this morning -- we're probably going to find that in the pre-pubescent group, the per kilo doses required to do this are going to be significantly higher than in the adult, the post pubescent individual.

So that we avoid the risk of under dosing and missing efficacy in that age group, and that could be done with a number of different ways, with traditional PK in a smaller number of kids or with pop. PK in a larger number of children, and that kind of information can be gleaned in the same protocol in conjunction with some safety, in the safety study.

One thing I've seen that I'm uncomfortable with is laying out a whole sequence of studies, one to do PK, one to do PK/PD, and another one to do safety and maybe efficacy in the population.

I think with a finite population of children to work with, we have to try to get as much

information in a study as we can without overburdening it with doing too much in one protocol. But I think that one mistake that we tend to make is -- and I think I've seen it in some of these proposals -- is we have a protocol for every single type question we're trying to answer, and we're doing things in some of these samples of kids that we wouldn't need to do if we combined some of the protocols.

But I think in terms of PK, we ought to aim at exposure, looking for differences, gross age related differences. These are drugs that appear to have a very wide therapeutic range, a very large therapeutic index. So it's not like a drug that has a high toxicity or toxicity very close to the concentrations or exposures that you need for therapeutic effects. So we have some room to maneuver here.

CHAIRPERSON CHESNEY: Dr. Kerns is another PPRU representative.

DR. KERNS: I'll try not to make this sound like the Kansas City mafia.

Exposure response guidance I mentioned

earlier hits right on the head with what Dr. Kauffman just said, and, Victor, you know, do these studies, have a role. Are they important?

I think it's very clear that if you look at the exposure there you see these drugs, and if you look at their ability to work in a single dose, there is an association there. It's clear now.

Now, what happens with multiple dosing with respect to the PD is not known. PK with multiple dosing is pretty boring because the drug is not there.

The difficulty with the PK/PD studies, and we've participated in a few of these, is that if you look at most of the PPIs, they are not pharmacologically clean substrates. These are polyfunctional substrates for cytochromes P450, 2C19, 3A4, which means when you look at the variability of the data, which was actually reflected in Dr. Hassall's J.Peds. paper when he reported the wide range of doses, what you really had there underneath it all was AUC had a huge range, a huge range, with the same milligram per kilo dose.

Now, if you go back to examining the

impact of ontogeny on the pathways, you can't look at a benzodiazapine examine for 2C19, which was mentioned earlier, and make since out of omeprazole because a huge amount of it is biotransformed in the small intestine where it's also a P. glycoprotein substrate.

So a lot of what falls out in the relationships between PK and PD is the fact that there's so much variability. Now, let's try to separate age out of all of that. Let's try to get to ontogeny.

But we've first got to get to pharmacogenetics. How many studies of any of these drugs in pediatric patients have you seen include 2C19 genotyping or 2C19 phenotype assessment?

And the answer is in the public domain, zero. Now, that's important, especially if you're doing the study in San Francisco where you've got a huge percentage of Asians. Okay?

And I bring this up not to add controversy, not to put kerosene on the fire, but to say to sit around and talk about designs that ultimately have to get to exposure effect correlate,

you have to be able to tease out the impact of age, and it has to be done effectively.

One of the limitations of pop. PK, even though it's part of the template, and I applaud that, population PK can be very useful as long as you've got a drug where the variability is small.

but when the variability is huge and you have no idea how to parameterize the model, you could wind up with, you know, kind of dog food at the end of the day and no answers that will really help children.

So these studies have to be designed very critically, carefully. They have to take into consideration the impact of growth and development on the disposition of the drug, and by all means, the exposure response stuff is critical because if the drugs work on the proton pump in a reliable way, in a reproducible way, make the exposure the same.

And as Dr. Kauffman mentioned, these drugs are not digoxin. You know, to give you an idea, omeprazole at a .4 milligram per kilo dose makes the same range of AUC, which is 240 to about 2,200 nanograms per mL per hour. Okay? Do you get the

picture? Tenfold, one dose tenfold as the 30 milligram dose does in adults.

And the thing of it is when you look at the PD part, just as far as acid suppression, they both work the same.

CHAIRPERSON CHESNEY: Thank you for that great clarification.

Now we have to start doing genetics. Very, very, very interesting. Any other comments before we turn to our -- yes, Dr. Danford.

DR. DANFORD: I'm wondering particularly about the designs that involve pharmacokinetics in the under 44 weeks corrected gestational age population. If we've just spent the morning discovering that we have a poorly defined disease that we're treating and indications that are very murky, and we don't even know how to design the efficacy study to show whether it's good or whether it causes adverse effects, what are the ethics of exposing premature infants to these medicines to learn their pharmacokinetics?

CHAIRPERSON CHESNEY: I think that raises the whole issue of the immature GI tract, and there

have in some animal models been associations with malignancy. So I think that's a very concerning issue also.

Dr. Murphy and -- no, I'm sorry. Dr. Kauffman.

DR. KAUFFMAN: This is not pharmacokinetics. I sit here watching us as we have for decades degenerate into research therapeutic nihilism because we can't figure out how to do it perfectly, and so by default, we're going to make the greatest ethical mistake, and that is to continue giving these medications to kids without any information, where we've been told by some people, particularly neonatologists, that there is a way to do this to at least get some information so that we're not completely in the dark.

Sometimes a candle is better than nothing, but it's not a spotlight, and it's a candle, and maybe we're striving for a candle here and that's the best we can do, but it's certainly better than being completely in the dark.

And I think too often we have allowed

ourselves to by default end up doing the most unethical thing, and that is continuing to expose children to medications without the kind of evidence we should have.

We're all applauding evidence based medicine. It's hard to practice when there's no evidence.

CHAIRPERSON CHESNEY: What I think I've heard this morning is that, from the people who have been using these proton pump inhibitors now for years, is that what they need is the PK and PD data. That's what I thought I heard very clearly. So it seems to me like that's a given.

I think the area that we are least sure about is this association of respiratory manifestations with reflux that we do see in premature infants and in some term infants that ultimately come to reflux surgery. And I think that's for me where I'm not -- Dr. Spielberg is always much more eloquent than I -- but that's where I'm puzzled.

But the PK and PD data, it seems to me, we need, and I agree with you. To me it seems like

that's a given. We should absolutely do that.

Dr. Santana.

DR. SANTANA: But I think the additional safeguard for that very young age group is that we do like, for example, we do with a lot of HIV trials. We try to get as much information to establish the relationships in the older populations first, and then once we clearly have identified those relationships, then we start exploring them in the much younger age groups to try to minimize the risk and safeguard them.

So it's not you do it. It's the timing of when you do it, I think, with good information to minimize that group.

So it needs to be done in that group because Ralph is correct. If not, we're not going to learn that, but we minimize it by getting the information on the older age groups first.

DR. DANFORD: I don't disagree with anything that Dr. Kauffman or you just said. I raise the question of whether people like Dr. Nelson are going to let us do this.

(Laughter.)

CHAIRPERSON CHESNEY: Dr. Raczkowski and Dr. Murphy.

DR. MURPHY: I mean, one extreme, which I don't think anyone wants here, is that we don't have enough information to really understand as fully as we all would like as scientists and physicians, and therefore, you know, the agency should just not issue anymore written requests and wait until NIH funds the studies and we all have precise understanding of what might be the best endpoint.

And I think that clearly is not what we want to do. We have always said that we understand for all of the reasons that have been stated that our knowledge base is not what we wish it to be, but it's our responsibility to try to improve that knowledge base.

And then we want to do it in the most ethical and most hopefully enriching way as far as information is concerned.

Clearly, this is a difficult area, and I said in the beginning we brought this to the committee because we feel that what we have asked for in the

past, we've learned that we think we have more questions. That's exactly what happens, is that as you move forward and begin to study children, you actually have more questions.

And we think that we need to develop in the older age group the better dosing information and better relationships between the dosing and the outcomes.

I think that for the older population the committee appears to agree with us in that area. I think that the issue here that we're all struggling with and we've heard both sides of this argument, which is that we don't even know enough to design the trial or that the people, the neonatologists feel that they do know enough to at least give us their best assessment of what the endpoints should be.

And where we're really struggling is because of that limitation in our knowledge of what the best endpoint may be is what is the best trial design in how to define moving forward with getting information whether there is this relationship or not.

And I think one of the things that we may

need to consider here is as we go forward in the older age groups with potential PK/PD studies, would be instead of waiting completely is to ask is there -- and we've done this. In some ways this is what PK/PD is, one could say, but it wouldn't really be. It would be more of the outcome type of study -- would be can we define maybe a test of our hypothesis in this young age group, that the trial should be a test of whether we have the right endpoints or not instead of going for the complete question of efficacy.

I think that might be something that we have not really considered as extensively as we may need to at this point.

Another question that was put to me by medical officers during our discussion would be if we said for the younger age group -- and I'm going to just not even put a date, age on its right now -- somewhere below six months down to a weight that one can keep alive, if you will, in the preemie; if we don't do an efficacy trial, what are the most important questions that the neonatologists would want us to try to address?

I think that that might help us work on this some more, think about it some more. So I Don't know if we actually have time to go around to ask that, but since Bob isn't there, how many neonatologists or others do we have? If we could ask you to think about that and provide us some input on that.

CHAIRPERSON CHESNEY: Well, we have at least two neonatologists and Dr. Spielberg.

DR. SPIELBERG: Let me try to take a quick crack at it because I think what Ralph said is the heart of what we're all here about, which is to shed maximum light in often very, very difficult situations.

There's no question but that one of the issues in the preemie is formulation. You know, these compounds by definition have all kinds of problems. We talked at the break about even in nursing homes of crushing omeprazole and putting them down G tubes so that no one gets efficacy.

So we need a formulation that works, and in that context, we need good PK on that formulation,

and we need good PK/PD on that formulation so that if, indeed, we are going after an acid suppression mechanism, neonatologists are going to know how to do it because that's the first key thing that we want to understand here.

Can we suppress acid appropriately, safety? What are the doses? And how do we administer it accurately in the volumes required for these small babes so that they, in fact, receive the drug in an appropriate way, recognizing that GI absorption, all sorts of things may differ here, and we've got to get that part of the story down for sure.

If we went ahead, regardless of what kinds of efficacy studies, be it carefully done PK outcome studies done by NIH by the Neonatal Network or whether it be sponsored studies, we need the formulation, the PK and the PD, before we even start off so that we know that those trials will have optimum control of acid if the question is: is acid suppression going to lead to the outcome of concern?

So those things I think we for sure need, and are very reasonable to do. Then the question is

the efficacy trials and are they ready for prime time. Do we need more now?

In my heart of hearts, just looking at what I would try to design, I think we do need more because, again, I mean, the thing I'm most fearful of is doing a study that's negative because we've really picked -- and we'll never get to do it again. I mean, you know, we're not going to be able to do it or --

DR. MURPHY: Steve, I don't agree with that. You know, maybe -- maybe --

DR. SPIELBERG: Well, I am concerned because --

DR. MURPHY: Bob can kick in here, but I mean, we do negative studies. We get negative studies, and we go on and do more studies because we know that one negative study does not constitute the answer all the time, and some time in that negative study we actually learn quite a bit about how we need to do the next study better or what we shouldn't do in the next study.

DR. SPIELBERG: Yeah.

DR. MURPHY: So I don't want people to

leave the meeting saying because we have one negative study that we'll never do another study.

DR. SPIELBERG: But in peds. it is all the more critical because of patient numbers and because of other interventions.

DR. MURPHY: But particularly if you have efficacy.

DR. SPIELBERG: We're beginning to chew up the number of neonates with different drugs that we're going to be studying. So we do have to be careful.

It's not to say we shouldn't do it. I'm just putting out the cautionary note that I'm not sure how I would design the study now. Maybe some additional data really would provide us the basis for doing it, but regardless, formulation, PK, PD, that's going to be the basis of any of the studies.

CHAIRPERSON CHESNEY: Dr. Blackmon and Dr. Hudak, you've been on the hot seat all morning. Responses to Dr. Murphy?

DR. BLACKMON: I don't know that I have a good answer for her in terms of what we need beyond what he's already outlined. A background study, and

I'm not sure that this particular step in it is really the issue as does acid reflux have a significant etiology role in apnea and bradycardia that is of serious nature.

Let me say right off the bat I do not think it is a part of apnea prematurity, which is a mandatory drive, maturational problem. It has nothing to do with that.

I do believe that a study could be designed to answer that question and measure efficacy. It would require a very large, multi-center population to do it because I think the numbers of infants in which that is the probable etiology are relatively small in an already small population of very premature infants.

CHAIRPERSON CHESNEY: Dr. Hudak.

DR. HUDAK: Well, I would just echo Lillian's comments. I think that, I guess, to give some idea of the number of patients that might be eligible with the criteria that we sort of loosely talked about, my nursery that has about 600 -- two nurseries that have about 600 admissions a year a

piece; we probably have about two to three babies a month to be eligible in centers that large.

So the need for a good, multi-center study is clear, and I think, you know, the formulation PK/PD data are critical.

I would also want to very carefully look at the known adult toxicities and just make sure that we look at those matters in the babies that are dosed, you know, whether they're related to possible hepatic issues or whatever, but just to design it where we look at some sort of a chemical safety profile while we're at it, if that's relevant.

DR. RACZKOWSKI: I want to thank the committee for all of their considered discussion. It's been extremely helpful, and we've held you back from lunch, but it's been very, very helpful to the agency, and on behalf of FDA, I want to thank everyone, including the invited guests.

CHAIRPERSON CHESNEY: Could I suggest that we reconvene at quarter after two? That would be an hour.

And I would also like to thank everybody

who made comments today. I think this has been extremely interesting, and everybody here added yet another piece to this puzzle. Thank you all very much.

(Whereupon, at 1:07 p.m., the meeting was recessed for lunch, to reconvene at 2:15 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:21 p.m.)

CHAIRPERSON CHESNEY: I'd like to start with a few administration issues.

Dinner is on our own tonight. Use your salary that you got today for dinner tonight.

(Laughter.)

CHAIRPERSON CHESNEY: Tomorrow morning's meeting starts at nine o'clock, and if we could all meeting in the lobby at 8:30, we'll arrange to have taxis there so we can take group taxis to the FDA.

Be sure to check out of the hotel in the morning and have your luggage to take with us, and --

DR. SPIELBERG: Joan, for those of us not staying here, what time are the taxis going to leave the hotel?

CHAIRPERSON CHESNEY: We're ordering them for 8:30, and I guess we'll probably need more than just enough for bodies because of luggage maybe.

The training will end at two o'clock tomorrow afternoon for those of you with or without plane reservations that can be modified.

And one other announcement. Dr. John Walkup from Johns Hopkins is part of our group today, and he can hear us and we can hear him when he speaks, but otherwise, we won't know that he's there; is that correct?

DR. WALKUP: Yes, that's correct.

(Laughter.)

CHAIRPERSON CHESNEY: Thank you.

Tom Perez was just telling me I should ask you to say something, and I hadn't quite made it that far.

So this afternoon we have a very interesting collection of issues to address, and I guess -- I don't know, Dr. Murphy, if you want to make introductory comments or Dr. Roberts, or should we go right away to Dr. Willoughby?

DR. WILLOUGHBY: Okay. Thank you, Dr. Chesney.

I'm Anne Willoughby. I'm the Director of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development at the NIH.

And it's a pleasure for me to join my FDA colleagues today in discussing some important issues with the distinguished Advisory Subcommittee.

As you all probably know, it's stated in the Best Pharmaceuticals for Children Act that not later than one year after the date of enactment of this Act, the Secretary, acting through the Director of NIH and in consultation with the Commissioner of FDA and experts in pediatric research shall develop, prioritize, and publish an annual list of approved drugs for which there is no patent protection or market exclusivity.

The act goes on to state that in developing and prioritizing the list, the Secretary shall consider for each drug on the list the availability of information about its safe and effective use, whether new information is needed, whether new pediatric studies concerning the drug may produce health benefits in the pediatric population, and whether reformulation of the drug is necessary.

So we're talking about the generation of lists here. What list or lists are we talking about?

From an implementation point of view, there are two. That is, there's a preliminary priority list that contains a number of drugs that are slated for consideration and evaluation starting in fiscal year 2002.

My FDA colleagues, Dr. Rosemary Roberts and Dr. William Rodriguez, will present the considerable work that permitted the development of the preliminary priority list of drugs.

After their presentation, I'll briefly summarize the role of NIH in the further refinement of this 2002 preliminary priority list.

I'd like to underscore the fact that the preliminary prioritization list by FY 2002 is intended to accelerate the implementation of the BPCA. So we're talking about a list that's already here and we're going to present today.

The other lists refer to the new annual list that shall be published in 2003, 2004, 2005, and 2006 of drugs prioritized for study in pediatric populations.

The process for the generation of these

annual lists that will follow the list we'll present today for 2002 will insure that the periodic examination of new knowledge and the identification of new needs with respect to drugs for use in the pediatric population will occur regularly.

At present, the process for the generation of these annual lists has not been specified.

It's my pleasure right now to turn to Dr. Rosemary Roberts who's going to present the considerable background that permitted the generation of this list.

DR. ROBERTS: Good afternoon and thank you all for being here and thank you, Dr. Walkup, for teleconning in.

And I wanted to just talk to you about yet another list. You know how much we loved the last list. Well, if you don't, you will know as I get through this talk.

Next slide.

So I'm going to go through the various lists that we've had to date and then end with the off-patent list, which is our charge here today to

talk about a process for developing that list and prioritizing it.

Next.

Now, the first list was actually started to be worked on in 1995, and that was by a working group of the initial pediatric subcommittee that was formed in December of 1994, and in your packet you will see this two-pager, and all it does is it just talks about how this list was developed.

And the charge of this working group was to identify drugs that are most widely used in pediatrics on an out-patient basis for which there was inadequate use information.

And some of the general findings they had were that in the population less than two years old, there was almost no drug that had any pediatric use information.

And for drugs that were used a lot in pediatrics for classes, categories such as for asthma, seasonal and perennial rhinitis, which are very commonly used in children, there was almost no information; whereas for the anti-infectives, there

did tend to be information that was collected by sponsors, mainly because of one of the bread and butter general diagnoses of the general pediatrician is otitis media. So there was always interest in developing antimicrobials for otitis media.

Now, the ten drugs that were on this list, and some are still on the list, were albuterol inhalation solution, and at the time this was put together, there was information on how to use this product down to the age of 12.

Subsequently, information has been -- this has been studied. Albuterol solution has been studied, and we currently have labeling down to the age of two.

Promethazine hydrochloride has not been studied.

And ampicillin sodium, this was a parenteral use, and remember this is out-patient data. This is from IMS, which is an international marketing survey company, and they have 2,900-plus physicians where they actually go into the offices and look at mentions of the drugs, and this was parenteral use of

ampicillin. It has also not been studied.

Auralgan otic solution for ear pain also has not been studied.

Clotrimazole betamethazone diproprionate. Actually the entire betamethazone diproprionate topical formulations have been studied, including the combination product with clotrimazole under the -- via written request, and that product is now currently labeled all the way down to birth.

Fluoxetine hydrochloride, or Prozac, has been studied. It's been granted exclusivity. We do not have labeling to date.

Now, cromolyn sodium, we do have a cromolyn sodium that's been studied, but it was a nasal spray that was studied for allergic rhinitis, and as an over-the-counter indication. What was referred to in this initial list was Ental or chromalin sodium for asthma.

Sertraline hydrochloride, or Zoloft, has been issued a written request, and those studies are underway, and may even come in. I'm not sure.

Methylphenidate hydrochloride, or Ritalin,

it was asking for studies below the age of six. It has not been studied to date via written request. WE have not issued a written request, and the reason is we really did not know how to study attention deficit under the age of six years. How does one consistently diagnose it? What criteria to use; what kind of tools for assessment.

The National Institutes of Mental Health currently has an ongoing trial looking at exactly that in the less than one year old.

Metaproteranol sulfaterol, Alupent, has not been studied to date. Information was needed on the less than six year old.

And beclomethasone diproprionate nasal sprays, written request was issued, but the studies were never performed.

So that's the first list.

Next.

Now, I'm going to talk about the FDAMA list, and I want to highlight some things, and Willoughby just read to you what the Best Pharmaceuticals for Children Act says as to the list

that was to be developed under the new act, and this comes directly from the Modernization Act.

Not later than 180 days after the date of enactment, which was 11/21/97, of the Modernization Act, the Secretary, after consultation with experts in pediatric research, shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population, and the list is to be annually updated.

Now, there are several areas of similarity in what we were charged to do by the Modernization Act. It was delegated to the Secretary, who delegated it to us. It was the Food and Drug Administration Modernization Act.

We were to consult experts in pediatric research as we are to do for the Best Pharmaceuticals for Children Act list. We were to develop, prioritize, and publish an initial list within 180 days.

We now have twice that amount of time to do it, and it was to be a list of approved drugs only.

It doesn't say anything about the status with respect to exclusivity or patent protection, and it was to be information that may produce health benefits in the pediatric population.

Next.

Now, the initial working list, we actually consulted many, many organizations and groups and got their recommendations: the American Academy of Pediatrics, PHARMA, the National Institutes of Health, the Pediatric Pharmacology Research Units, the National Pharmaceutical Alliance, the Generic Pharmaceutical Industry Association, National Association of Pharmaceutical Manufacturers, and the U.S. Pharmacopeia.

In addition, any drug in the orange book that had existing patent protection or exclusivity was put on the initial working list.

Next.

Then this working list internally, we divided all of these drugs that were now on this list, and it was several hundred. We determined which divisions regulated each product, and we then put that

on a list with the indications that were approved in the adult, and asked each of the regulatory divisions to look at the drugs on there and to see if they fit one of three criteria.

And really the first criteria is sort of like the definition we use for a priority review of a drug. Will it have a significant improvement compared to marketed products labeled?

Well, marketed products labeled, remember I just said most drugs weren't labeled. So it was not a problem here to be concerned about whether we had too many already in this category labeled.

"For use in the treatment diagnosis or prevention of the disease in the relevant pediatric population", so that was one criteria, or it was being widely used in the pediatric population.

For those of you that were here this morning, we know there's a lot of use of the proton pump inhibitors in the neonate, in the less than one year old, and that's part of the reason that's driving trying to study it, because it is being used.

And it was defined for purposes of this

criterion as at least 50,000 prescription mentions per year. Now, that dates back to the mentions we talked about in the IMS database, or it could be a class of drugs or an indication for which additional therapeutic or diagnostic options were needed in the pediatric population.

If a drug, according to the division that reviewed it, met any one of those three criterion, it was put on the draft list.

Next.

The draft list was published March 16th of 1998 in the Federal Register. So we actually got that out within four months of when the Act went into effect, and we asked for comments to come back within 30 days that we then had to review because we had to publish that list by May 20th of 1998.

Next.

There were 89 comments that were received. Many of them simply asked that a specific drug be added to that list or deleted from that list for whatever reason the commenter had.

There were several that said the criteria

that we used were far too narrow, and there were several that said one should include all drugs used in the treatment of diseases or conditions that occur in the pediatric population.

Next.

So what we decided to do after we reviewed those comments was to say that any drug that's approved for use in adults that's applicable to the pediatric population is on the list. That's a lot of drugs.

Now we had a challenge. That's the list. How do we prioritize this?

Well, depending upon which group you talk to, whatever drugs they need to treat their condition are the drugs that go on the list first, without a doubt. But that wasn't helpful to us.

So next.

What we decided to do was that if you fit one of the three previously outlined criteria, you became part of the priority section of the list, and so we published this list May 20th of 1998. It was a bit large and unwieldy to deal with, as it had 400 to

500 drugs on it. And we updated it manually as we were mandated to do every May.

And that meant we removed drugs that were studied or had been labeled. We added approved new drugs that were for conditions in adults that were applicable to children. Also, industry could petition the agency to put a drug on, and we looked at those petitions, and if the petition was granted, we added that drug for the indications that they petitioned to go on with.

And then the division had a chance to relook at all of their drugs that they regulated to see if they had other input that had come in over the past year, if they had reasons to take it off because of some safety concern that had developed, et cetera.

So it was not an easy task to update this every year. It took an awful lot of resources by the agency to do this.

So what if you were on the priority section of the list? What did that do for you?

Well, it didn't constitute a written request. So we still had to write a written request

if you were on the list.

It didn't mean that you would quality for pediatric exclusivity, and there could be several reasons. One, you may not do the studies that were asked for in the written request.

Two, it may have been for a product, like an old antibiotic, that didn't have any exclusivity or patent protection to which pediatric exclusivity could be attached.

And the sponsor wasn't required to do the studies in the written request. So what exactly it did to be on the priority list is questionable. So it didn't help us in prioritizing, we learned, because we couldn't get a consensus.

So we ended up with a long list that was unwieldy. It's a voluntary program. So why prioritize the drugs that need to be studied when you're going to issue the written request, and if industry is interested in doing it, they'll do it, and if they're interested in doing it, they'll also send you a proposal and indicate to you they want to do it as we've now received over 300 proposals since June of

1998.

It was resource intensive for us to update this list, and while we're updating the list, we're taking the same people that are supposed to be reviewing the proposals, reviewing the supplements, and now we've got them updating the list.

So overall the list wasn't helpful from our point of view, and actually in the report to Congress that we were mandated to write and that we submitted to Congress in January 2001, we recommended eliminate the requirements for the list.

Next.

Then at our request, we asked the American Academy of Pediatrics for their suggestions of drugs that are most frequently used by pediatricians in the care of their patients and for which additional information is needed.

And Dr. Rodriguez will talk to you about that list and how it has subsequently been used in putting together the preliminary priority list.

Next.

Other lists historically, the USP has

looked at available information, pediatric information for products that are used off label in the pediatric population, and post enactment of the Best Pharmaceuticals for Children Act, the USP has put together a list of off-patent and off-label drugs that have narrow therapeutic indices or for life threatening diseases and are being used in the pediatric population.

Next.

Now, we have the Best Pharmaceuticals for Children Act, and what I can say is that Congress did listen to us. They did read our report, and they did some of the things that we asked.

They eliminated the list. However, in the next section they created a new list.

(Laughter.)

DR. ROBERTS: And this is a list to study off patent. So in order to be on this list, and the criteria that are outlined in Section 3 of the act, most of those criteria refer to the fact that you have to be off patent and have no exclusivity remaining. So you have to have an approved generic application or

have submitted one and qualify to get a generic application.

So we are now mandated to do a new list. Now, they created a research fund. They authorized appropriations of $200 million for FY 2002 so we could do these studies, but we got this much in the budget to do them. So we got a research fund authorized, but not money yet.

Okay. Next.

Now, this is what Anne just read to you, and now we have a year after the enactment, which was January 4th, 2002, and now NIH is in the lead. They're to consult with the FDA and experts in pediatric research, one of the reasons that we're here today, and to develop, prioritize, and publish an annual list of approved drugs for which -- next -- now, the drugs on this list I want to emphasize are to have no patent protection or market exclusivity. That is, they are not listed in the orange book, and they need additional studies to assess the safety and effectiveness of the use of the drug in the relevant pediatric population.

Next

Now, in developing and prioritizing this list, we are to consider for each of the drugs availability of information concerning the safe and effective use in the pediatric population whether additional information is necessary, whether new studies concerning the drug may produce health benefits in the pediatric population.

Now, I want to remind you this is exactly the same charge as we had under the Modernization Act. We are to assess whether the drug, if studied, may produce health benefits in the pediatric population, and whether reformulation of the product would be necessary to study it in the pediatric population.

Next.

Okay. Now, other things that are outlined in Section 3 is the pediatric study that is to be done on these off-patent drugs, and it directs as to how this process is to be completed.

FDA, in consultation with NIH, is to remain in the driver's seat and write the written requests for these off patent drugs, and once the

written request is written, we are then to issue it to not only the innovator, if there's still an innovator in the market, but to all approved drug holders of that drug.

And they then, within 60 days, are to let us know whether they agree to do the studies that are outlined in the written request. So they get 30 days for the first right of refusal. If none of the holders of the approved applications agree to do the studies, then it will get referred over to NIH, and those holders of the approved application have no right then to bid for the contract.

NIH, in consultation with FDA, shall publish a request for contract proposals to conduct the pediatric studies that are described in the written request.

So thank you very much. Dr. Bill Rodriguez, Director of Science in the office, is going to talk to you about how we put together this preliminary list.

DR. RODRIGUEZ: Thank you.

It's interesting that one list led to the

other, and what you're going to be hearing about very soon is the hybrid culmination of lists.

Next slide, please.

Giving equal time to everybody was very important to demonstrate that not only do we produce them from within, but we also get some of the information from our resources that are in the community.

And essentially in July of 1999, Dr. Robert Ward, who was chairing the Committee on Drugs of the American Academy of Pediatrics, provided a list back to the FDA, a list which actually had now information from current use by pediatricians. Essentially it had information in terms of ranking which actually have been provided after written and oral requests from the committees, the sections, and also from publications in the American Academy of Pediatric News of general pediatricians in the community.

So essentially that information was provided, and there were three categories, priorities that were ranked in the list, and essentially what I

did was, if I could have the next slide, please, was first of all to alert you that these were patent and off-patent drugs together, and remember our current mandate is to look at the off-patent drugs.

There were 281 drugs that were ranked, and we concentrated on looking at the 126 drugs in priority number one or the highest priority.

It's interesting to keep in mind that that, again, is a combination of patent and off-patent drugs, which was exactly the way that the FDA priority lists of '98, '99, 2000, 2001 was composed. You had patent and off-patent drugs in there, too, usually to a ratio of three to four to one.

Next one, please.

We also used other forces, and as you heard Dr. Roberts speak to you earlier, we used some of the IMS data and also that essentially listed a number of the top ten drugs, and it's interesting again that of those listed in '94, some of them had actually now been labeled, and number two, some of them had received written requests.

So some progress was going on, but there

were still four in there that did not have a written request, didn't have any labeling in pediatrics, and again, were listed as very high in terms of use.

Could I have the next slide, please?

So this thing which may not be very readable, but which was provided to you all in your pre-meeting package and it's available again in a more completed version in Dr. Murphy's handout essentially took a look at the top drugs that were listed, including the ones that were in terms of use and not in the FDA list.

It included also information that had what's available. As you can see, there are age groups in which pediatric information is needed essentially from our 2,000 lists of drugs and essentially addressed the divisions in there that were responsible for the specific drugs.

As you can see, some of them were not in the FDA priority list, and you can see the check mark next to it.

Next slide, please.

So now we have sort of a, quote, unquote,

priority list that is provided to the divisions for input. So essentially they would be able to tell us, "Wait a second, you know. This information is missing, and therefore, this should not be used," or, "we should add this or we should subtract this," so essentially trying to capture as much of the information as we could since we were moving forward in this process.

And we ended up with a preliminary priority list that, quote, unquote, is listed in there that included prior Academy of Pediatric lists, the FDA updates in these divisions, and some of the information from the IMS and Children's Hospital Corporation of America data.

So this is now updated to 2001, and Dr. Murphy will be going into this further on when she speaks to you all.

So the third thing that we did -- I mean, the other thing that we did is in the next slide. We provided this preliminary priority list to members of an ad hoc expert panel of the NIHCHD, which represented individuals with, well, recognized

expertise of various walks in the pediatric field, and they were to look at it, and Dr. Willoughby will be actually going over the next iteration. As you can see, it's a work in progress, and it will continue to be in progress for a while.

Thank you.

DR. WILLOUGHBY: I think one of the things that is absolutely clear is the list that we're going to talk about today stands on the shoulders of innumerable individuals who have been doing a lot of work in this area for many years.

So NICHD took the list of 19 drugs that Dr. Rodriguez has just told you about, and we convened a panel of experts in pediatric pharmacology and people expert in the use of drugs in pediatric populations in April of 2002.

These experts included Dr. Ralph Kauffman, Dr. Richard Gorman, Dr. Lillian Blackmon, Dr Robert Ward, Dr. Philip Walsen (phonetic), and Dr. Wayne Snodgrass.

The federal staff present during the consideration by these experts of the list of 19

included Dr. Dwayne Alexander, who is the Director of the National Institute of Child Health and Human Development; Dr. George G. Akoya (phonetic); Dr. Gilman Grave; and Dr. Bill Rodriguez from the FDA. And, of course, several of the people I've just mentioned are present today.

The group was briefed about much of the information that you've just heard, and they were told that the purpose of the meeting was to review and analyze this preliminary list of 19 drugs and then also to identify other drugs that merited additional study in pediatric populations in their opinion.

It was emphasized that the prioritization should be objective and evidence based, and that the needs of children in different age groups and subpopulations should be considered.

Dr. Kauffman chaired the meeting and led the group discussion. He began by stating that the PIs, at the Pediatric Pharmacology Research Units had in 1999 reviewed off-patent drugs in need of study, and that they had considered most of the drugs on this list of 19, and there were four in addition which they

believed merited consideration: ketamine, amphotericin B, bumetamide, and morphine.

Dr. Richard Gorman commented that nonionic contrast agents had not been studied in pediatric populations, and then the group also mentioned that methotrexate, because of its prominent role in the treatment of autoimmune diseases ought to be considered.

The group also agreed that they wished to consider diazoxid in the treatment of hypoglycemia be included on the list.

So after considerable discussion, and I have the record of those discussions, if the committee would like it entered into the written record of this meeting, the experts were asked to individually, after discussion with each other, but not in consultation with each other, to privately prioritize the group of drugs from the list of 19 and also from the drugs which had been added to the list early in the discussion, that is, the four drugs recommended by the PPRU, the nonionic contrast agents, methotrexate, and diazoxide for the treatment of hypoglycemia.

The individuals at that meeting voted separately, and what emerged was what we have chosen to call the highest priority cluster, and then the next highest priority cluster.

In the highest priority cluster are dopamine, lorazepam, doputamine, morphine, acyclovir and ketamine.

The next highest cluster includes nonionic contrast media, amphotericin B, nitroprusside, and valproate.

The remainder of the drugs are arrayed on a lower priority list after that.

Now, the reason we are considering these to be a cluster is it isn't possible or reasonable to say, "Here's drug number one. Get it off the blocks. Here's drug number two. Get it off the blocks."

Rather we have this cluster which were are going to partner with the FDA in working on through the process that Bill and Rosemary have described in order to see that studies are initiated on these drugs in pediatric populations.

And so that essentially is our working

preliminary list. Now, you might say, "Well, why rush to a list in this fashion?" although if you consider the background of it, it maybe is not as much of a rush, and that's because the secretary has committed to obligating funds in FY 2002, which ends at the end of September to study drugs on this list.

So there's a lot of process even with this preliminary list that needs to be gone through involving the written request and potentially the generation of RFPs.

So that was the process that brought the 2002 cluster of prioritized drugs to the table today.

CHAIRPERSON CHESNEY: Dr. Murphy.

DR. MURPHY: What we are going to do is to try to talk a little bit about criteria that we have been using and ask you for your assessment of should we continue to use these criteria, should we expand these criteria, and any other comments you wish to provide us on how to move forward both in development of criteria and the process because those are the focus of the two questions really that we have for you today.

Next slide.

I am also going to talk a little bit about this set of 19 not because we want you to design trials for us -- no -- after this morning, but because we really want you to look at what's going on in the way the clusters look when you begin to apply these criteria of use and impact by definition of where we think the gaps are to that 19 so that you can see how it's beginning to play out when you address our questions that we're asking you.

Next slide, please.

One thing i did want to emphasize, and Rosemary did a good job of doing this, is that we have had a number of definitions under which we have been working as to how we decide what the benefit would be. One is the meaningful therapeutic definition which is under the rule, pediatric rule, and that definition is a significant improvement in the treatment diagnosis or prevention of a disease compared to marketed products adequately labeled for that use in the relevant pediatric population versus the definition under which we have been working for FDAMA and are

working in the present in the best -- I misspoke this morning and said "better." Forgive me. It's the Best Pharmaceuticals Children's Act.

So we do have this definition, "produce health benefits," and what we're asking you is beyond looking at the numbers of use and the missing -- identifying the gaps, are there any other criteria that we ought to be thinking about as we move forward in trying to define what is producing a health benefit.

These are some additional factors one might consider, and we would ask you to think about these and to address some of these as you answer our questions.

Certainly you've heard the need for additional options. that's important. That would be a positive factor in why one would develop a written request or wish to have studies conducted in children.

You need either a therapy studied or additional therapy studies in serious and life threatening disease, and in pediatrics we have many orphan populations. Not only is all pediatrics

considered an orphan population, but certainly the neonate is another subpopulation, nd certainly rare diseases within the pediatric population continues to be such populations.

Negatives from our perceptive, the "me, toos." Do we really need a 15th cephalosporin study in children? Some would argue yes, but that is something I think that what is the definition of enough?

I hear somebody say this morning after we have one we shouldn't issue anymore. I think you would get quite an argument on that, that patients can't all tolerate the same product and that's why we do need options.

A product may have a higher adverse event or a rose adverse event profile, but if it's the only other option, maybe we do still need to move forward in asking for studies for that product.

A narrow therapeutic index when alternatives are available might be considered a negative reason or a reason not to issue a written request.

Next please.

So our criteria to you, and we're going to stand down here in a minute and ask you to address these. The questions are: for the criteria that we should use in thinking about developing these lists, should our volume, how often these products are used in children -- again, we've heard many products are used quite a lot without ever being studied. How important is that criteria?

It is mentioned in our rule. It's mentioned in a number of places as being something we should evaluate.

The impact. I've indicated that the impact definition right now is produce health benefit. So how do you really define impact?

Are these two criteria adequate for selection of drugs for the list to be studied, parts to be studied that are off patent?

And if yes, if that's sufficient, those two alone, would you help us with the definition of produce a health benefit? Any other thoughts about how we might define that?

And if not, why not? What other additional factors would you consider? Just some of those that I put up on the slide, if you would.

Second would be process. Anne and Dr. Roberts and Rodriguez and Willoughby have described a process here. What do you think about that process? We'd like to have your thoughts about are there other sources the FDA and NIH should consider in the development of the list.

And is there any weighting to this process, if one wants to get really precise about it or not?

Next.

The priority list must be produced by January 4th, 2003. What are the committee's recommendations for facilitating timely input into the development?

You've heard about how extensive input has been sought in the past. You've heard about you can get ten different groups in this room and depending on the disease of the group that's representing you will get ten different lists.

We do clearly seek input, but we also need to have input in a timely and effective manner that allows us to move forward so that we can have products on this list that get studied. So we wish you to balance that in your consideration today about what process do you think would facilitate input of this committee into development of a list.

And in addition to that process for this committee's input also, how would you like to have your updates, if you will? What do you want to hear about? How much detail you want to hear about the studies that were conducted.

Certainly I would think you would want to hear about what labeling has been resulting or not resulting, but we'd like to hear what is of interest to you in feedback on an annual basis.

Now, I am not going to ask for discussion on the 19 items that we're going to -- well, actually 18 because I left auralgan off. I'm going to go through them very quickly, and we don't seem to have a pointer.

So I wanted to just to through with you --

does somebody have a pointer? No? -- what these products look like when we applied use data from the children's health center database that has been newly developed. I want to please lay out the caveats about this database.

These are absolute numbers. They have no projection methodology associated with them, unlike the IMS data. So what I'm telling you is the numbers that you see under the CHC data reflect literal absolute numbers for 25 -- is it 25 or 29, Rosemary? I think it's 25 hospitals that range from free-standing children's hospitals to hospitals within larger complexes, and it's from their pharmacies basically.

So those are absolute numbers without projection methodology applied to them, while the IMS data is data that is mentioned and has some projection methodology associated with it.

Thank you very much.

So we have for cardiorenal these five products that have been identified as needing further study in children. You can see that within those 25

children's hospitals diazoxide is not used very frequently compared to dopamine. I think that's a level of comparison that you can use this data. That's about all you can do, is just look within the data to compare high use to low use at this point.

We also don't have any IMS data on this. Remember IMS is out-patient. It's one of the reasons we have worked for two years now piloting what mix of hospitals we need to try to get sensible data on pediatric in-patient use, because some of the databases we're using were really adult based databases, and when we saw that they had no use of albuterol in the various pediatric age groups, we knew we had a problem.

So this database was developed, again, to focus on in-patient databases of pediatric hospitals.

And the missing information that's been identified is really from birth to 16 years for all of these for use in hypertension, hypertensive crisis or for digoxin for very specific arrhythmias.

We handed out to you just so you would have it to compare as you think about this the actual

indication associated with each one of these products, whether it has any pediatric information at all, which included a comment in the pediatric subsection or the dosing section.

And we have a new medical author, Suzanne Olness (phonetic), who put this together in the last 48 hours because we realized, you know, we were familiar with this list, but maybe you guys wanted to know what is actually in the label for these products right now and whether they have any information at all.

So that is also part of the information we provided you.

Next one. Go back one, please.

I can tell you that right now we are looking at a product out of this cluster to begin development of a written request.

Next.

For neuroform, and I have clustered these because over and over again if you look at either exclusivity or the products on this list, these are two of the areas which consistently we have indication

that not only is there a large amount of use in pediatrics, but also a need to have priority study.

So in here we have use that, again, this is in-patient data, varies from in the hundreds to the thousands, 16, 17,000 prescriptions for lorazepam versus our out-patient data, which again is higher, which you might expect, for the some of the treatment ADHD and lower for some of these other products. The promethazine has been on our list for a long time.

Somehow this got left off, but this is supposed to be less than two year old. The missing information is less than two year old for controlled nausea and vomiting associated with anesthesia.

And I can tell you that we have already looked at one product on this list, which it turns out for technical reasons I won't go into, but that we really can't issue a written request for it because actually part of the molecular entity may still be under patent, and we are now actively looking at a second product on this list to issue a written request for studies for this product in the neuropharm are.

Next, please.

Quickly, again, just to demonstrate the same sort of thing here in the pulmonary data and the fact that the missing information is birth to six year olds for bronchospasm has been the identified gap.

Next please.

Antimicrobials, again, we have already looked at one product on here which we will not be issuing a written request, or sometimes as you dig into these more deeply, you find that there are actually other data that you may want to develop or seek in another way.

So it doesn't mean that being on the list you will always get a written request.

And next one, please.

End up with GI, sine that's sort of where we started this morning, and as you can see, a very high use here for metoclopramide, well used for cimetidine.

Next please.

And that is a quick run-through of the 18 products that are presently on the list. It does not include the additional products that the NIH expert

panel recommended because we really felt that we want to demonstrate that those were additional products that were brought up, but we wanted to at least apply the data that we could and that we had on these to our presentation today on use.

With that, having run through what our present list looks like for us to begin development of written requests and what some of the use data looks like, what the gaps are, we would ask you to answer our questions on criteria and process to help us as we move through what is really a great opportunity if we get funding, if someone would find the money for the funding of all of these studies.

But let's be optimists at this point and say that they will assume they will, and we want to move forward with trying to get these products studied.

Thank you very much.

CHAIRPERSON CHESNEY: We have an opportunity at this time to hear anybody who would like to speak in the open public hearing, and I understand we do have one speaker.

MS. HELLANDER: My name is Martha Hellander, and I'd like to -- well, you know what? I could do it from -- no, I'll come up to the podium.

Okay. Is that picking up?

Okay. I'm supposed to start with the financial disclosure statement. I never had to do this before. So it's my first time. I have no financial interest in any companies that make lithium products.

My organization, the Child and Adolescent Bipolar Foundation, has received some unrestricted educational grants from various pharmaceutical companies, including Solvay and GlaxoSmithKline in combined amounts not exceeding 11 percent last year and not to exceed five percent in our coming fiscal year.

I'm really here to represent children with bipolar disorder, and I have not even discussed this with any of our corporate donors.

I'm sure you're all aware that we've got a public health crisis in the making due to the recent enormous advances in our ability to diagnose children

with bipolar disorder and, on the other hand, the lack of evidence on how to treat them.

I'm here to urge you on this committee or the subcommittee to consider placing lithium high on the priority list for testing in children, and I'd like to urge the FDA to do at least a couple of types of studies that have never been done in children and are unlikely to be done by pharmaceutical companies.

The Child and Adolescent Bipolar Foundation is a parent-led, not-for-profit organization. We have about 5,000 families now in our first three years that have joined us.

Many of us have adults with bipolar illness and several generations, and recent advances in the detection of the disorder in children offer the hope of curing and perhaps even preventing this disorder at its earliest stages.

However, the data on treatment options are sorely lacking. We urge the FDA to take a leadership role in establishing safety and efficacy information on lithium, which is off patent and has been safety and effectively used in adults for over 50 years.

A little bit about myself as Executive Director of CABF. I've consulted on the design of treatment studies for adolescents with bipolar disorder. I'm the bioethics consultant to a multi-site NIMH funded treatment study.

I've participated in strategic planning for the Mood Disorders Group at the NIMH. I've served on an NIMH review committee for studies in child psychiatry, and I'm currently a member of the Pediatric Psychopharmacology Initiative Work Group of the American Academy of Child and Adolescent Psychiatry.

My husband is an academic economist, and one more thing. The disorder has caused suicides and ruined lives in many generations in both sides of my family, both myself and my husband's family, which are also filled with accomplished and creative individuals.

One of our children was diagnosed six years ago. Her suffering, early diagnosis, and remarkable recovery well before adolescence set me down the path to help others and brought me here to

speak with you today.

We've been doing some on-line surveys. We're a Web-based organization, and we've just got a new survey tool that I'm having a lot of fun with it. So we did our demographics.

So we have a rather, I think, interesting group of parents, very educated and resourceful. They have private insurance, access to great medical care. Our children are in good physical health. They're not living in poverty, and were born or adopted into loving families as far as I can tell.

Over half our members have graduated or intend to graduate from college. Twenty-six percent have graduate degrees. Most are married, and 50 percent of the spouses hold executive or professional positions.

Next slide.

I've included in the handouts an article by Dr. Barbara Geller that just came out in the American Journal of Psychiatry reporting on her two-year follow-up on a NIMH funded longitudinal study of about 90 pre-pubital kids with mania. Dr. Geller has

served as a consultant or a member of this subcommittee and is also the chair of our organization's professional advisory committee.

This is the ages of the kids. They're very impaired in many crucial areas of functioning, and to learn more about the suffering of our children, I'm not going to be able to go into a lot of the details, but please visit our Web site, pbkids.org, and you can learn more there.

Okay. These hospitalization rates, by the way, about 60 percent of our kids are under age 12. I want you to keep that in mind as I speak. The hospitalization rates are incredible.

Joe Bieterman at Harvard says that 25 percent of the kids that he treats have been in the hospital, and he finds that to be just really a lot.

More than half of our kids have been hospitalized in a psychiatric in-patient unit. So, you know, this is like the end result of not having been treated and helped by medication or treatment, whatever.

Okay. Next slide.

There's three grave public health concerns that I'd like to discuss with you today that intersect with childhood bipolar disorder and which are helped with lithium.

The first one is addiction, substance use. These kids appear to be biologically vulnerable to becoming addicted, and there's a cite, and the citations are to papers that are in the packet of handouts that I passed out, and I think there's some extra ones up here for people in the back that wanted to get a copy of those.

Next slide.

As I said, there's evidence that lithium reduces adolescent substance abuse and stabilizes mood in a randomized controlled trial by Barbara Geller. It was only a short-term treatment trial, ten weeks, but she found that lithium significantly reduced substance use and stabilized mood in these kids.

The implications of this finding are quite staggering, but it has been largely ignored by the substance abuse treatment community. I have no idea why.

Next slide.

When unstable, like adults with mania, bipolar kids are impulsive and exercise poor judgment. In one study in Texas by Steven Pliszka,, he screened 50 kids, subsequently brought into a juvenile detention center. Twenty percent of them met full criteria from a manic episode. Another 20 percent met full criteria for a major depressive episode, and I think two percent had a mixed state.

If the illness is detected early enough and properly treated, this outcome could possibly or probably, in my opinion, be avoided. So here's another public health crisis for kids that involves kids with mood disorders.

Next slide.

Dr. Geller also found, and many other researchers find the same -- she studied 90 pre-pubital kids with mania. A full 25 percent of them were suicidal on arrival at her out-patient clinic. There are pre-pubital. These are kids, you know, six, seven, eight years old with serious thoughts.

Now, I need you to add if you're taking

notes. Your slide may not say the serious thoughts, and when I discussed this with her, she felt that was important to put that in. I just had planner intent. So please note that.

Children often talk of wanting to make themselves dead. The don't know the word "suicide." So they say they want to make themselves dead starting as young as three or four, and they make real attempts, like trying to jump out of moving cars on the freeway.

This is the one thing that mothers compared notes, and almost all of them do that. So here's a third major public health crisis. Suicide is the third leading cause of death in the 15 to 24 year old range according to the Surgeon General that involves mood disorders.

Next slide.

Now, the 18 percent mortality rate, that's the lifetime mortality rate for this illness. That's higher than childhood leukemia. hat's higher than many cancers.

When I tell that to people, they can't

believe it because most people don't think of bipolar disorder as a fatal illness, but it is. I tell you we hear every day about young people killing themselves who have been diagnosed with bipolar disorder.

The studies that resulted in the 18 percent figures, and I think actually the one in the packet says 20 percent. I was going to cite Goodwin-Jamison, but I got that mixed up. They were not in adults, but many of the adults we know to have had early onset.

Okay. Lithium is known to reduce the suicide risk sixfold to eightfold. Kay Jamison said the other day -- she's a noted person who has bipolar and is an expert on it -- she said if those numbers cam out on a treatment for cancer, it would be the front page headline in The New York Times. There is a drug out there that is off patent that reduces the suicide risk six to eight times.

We've got 25 percent of our kids that are suicidal, and it does that -- lithium appears to do that even when it's not effective in stabilizing mood, which is very interesting.

No other drugs approved for mania have been shown to have an anti-suicidal effect, to my knowledge, and I could be wrong, but I think that's still the case.

Okay. Next slide, please.

As you can see from this time line, lithium has been on the market for over 50 years, and kids with mania have been described in the medical literature for nearly that long. Yet we still have no standard treatment for pediatric mania.

In your slide, I think I have in 2000 NIMH recognizes pediatric mania, but in fact, '95 was the year that they funded Barbara Geller's phenomenology and course study. So that was they first recognized it.

And then in 2000 they held a consensus conference on pediatric mania, and they agreed that you could diagnose it in pre-pubital kids using the DSM-4. So that was a landmark date as well.

We still have no standard treatment for pediatric mania.

In your handouts is a study by Elizabeth

Weller, just a sample. There have been a number of small studies, naturalistic studies, very, you know, promising and interesting, but not large.

Lithium was approved in 1970 for mania and maintenance treatment down to age 12, but at the time, no pivotal studies were ever done, and no post marketing surveillance studies or testing in juvenile animal models was ever done.

Next slide.

In a recent survey, our members reported over 40 different medications used to treat the symptoms of bipolar, none of which are indicated for children under 12, and only one, lithium, for adolescent mania.

Okay. This slide shows the number of medications our children have been prescribed during their lifetime, and these kids are mostly under the age of 18. I think there were a few 19, 20 year olds in there, but we had 854 kids of the 944 respondents to the survey. So 854 kids, and we asked each family just to respond about the oldest child if we had more than one with bipolar.

Trials of five, ten, and even 15 or more different medications are common, partly due to earlier misdiagnosis or confusion about the diagnosis.

But largely because even when they get the correct diagnosis, clinicians have no evidence based data to guide their treatment. We're getting frequent reports of kids being started on gabpentin, for example, as a first line mood stabilizer despite the fact that placebo studies in adults show it's not effective for treatment of mania and it has troubling side effects in children.

And I have a reporter calling me today who wants to talk to me about that.

Next.

This shows how many medications our children are currently talking to treat their symptoms and side effects. Let's see. How did I figure this?

Fifty-seven percent of our kids are taking three or more medications. Parents are faced with the terrible choice that they have a child with an illness that's life threatening and certainly impairing, and medications used in adults may be the only treatment

available, but we don't really know what the long-term side effects might be or which treatments might have a better long-term safety profile in which children.

So we have to take the risks, but we don't know what the risks are. It's a really difficult position to be in.

But when you have a suicidal eight year old, you know, there are certain choices, tradeoffs that you will make, parents will make. That's a pretty desperate place to be.

Just of interest, the current issue of the American Journal of Psychiatry had three articles in one issue on childhood bipolar disorder, and the editorial by Fred Volkmar writes, "The lack of treatment efficacy data on these conditions is most unfortunate."

Next slide.

Of the anti-convulsants, most are still on patent, except for tegretol. The same is true of the atypical anti-psychotics and the SSRIs.

We strongly support the further testing of all these medications in children, but I'm not

focusing on these other needs today since the topic of your hearing today is off-patent medications.

As you can see, lithium is being used in about 30 percent of our children, and I did hear yesterday, and I don't know if this is valid. I've been having trouble getting data on how many mentions or prescriptions are written. I heard 93,000 children in America between zero to 17 are taking lithium, but I don't know if that's mentions or, you know, currently or what.

Okay. Next slide.

In summary we believe that lithium meets all of the requirements of the Best Pharmaceuticals for Children Act, and that the urgent public health crisis of teen substance abuse, teen arrest and incarceration, and teen suicide, all of which include many kids we now know have early onset bipolar disorder, these crises call for lithium testing in children to be given the highest priority by the FDA.

In particular, we'd like to see post marketing surveillance studies and juvenile animal studies. We'd like to see requests made for these,

and if proposals are not forthcoming, we think they should be appropriated if and when funds are appropriated -- I'm sorry -- they should be undertaken if and when funds are appropriated by Congress.

Next slide.

I'd like you to take one more look -- this is my last slide -- at our Web site. The little girl with the blond hair and the yellow hat was suicidal at age four, but she's been well since age ten. She's 15 now, and in high school nd wants to be a therapist when she grows up.

The little girl at the top left is now 13, plays the clarinet, and has her black belt in karate.

Both of these girls stabilized when lithium was added to their treatment, which includes other medicines currently under patent.

The boy with the turtle is Ben Harrelson of Duluth, Minnesota. He had symptoms very early in life, and like most of our kids, was misdiagnosed with ADHD and conduct disorder. He finally was diagnosed with bipolar disorder and stabilized on lithium at about age 12.

That was about 15 years ago, and he felt really well, and he asked if he could stay on the lithium indefinitely, but 15 years ago there was no maintenance data to tell the doctor how long kids should stay on lithium, and guess what. There still isn't.

So the doctor cut back on his lithium to see if he still needed it. He relapsed and killed himself before they could get his lithium back to a therapeutic level.

So in conclusion, please urge the FDA to give lithium its highest priority for testing in children, and also, I offer to be of assistance if there's any way that our organization can be of help to you or to the NIMH in this effort.

Thank you.

CHAIRPERSON CHESNEY: Thank you very much for a very compelling presentation.

Dr. Murphy, should we take a break a this point or should we proceed with some of the questions or do you have any strong feelings?

DR. MURPHY: Well, I'm a terrible task

master. So --

CHAIRPERSON CHESNEY: All right. We'll move ahead.

DR. MURPHY: I would say let's move ahead and then maybe break right before we ask our European friends to speak if that's okay.

CHAIRPERSON CHESNEY: Okay. Am I reading the questions correctly, which are from your slides and the second two slides on page 2 and the first slide on page 3? Is that --

DR. MURPHY: That's correct.

CHAIRPERSON CHESNEY: Actually, Anne, could you maybe put the first question up? It has to do with criteria.

So we'll start with page 2, the middle slide. Yes, okay. Thank you.

Are volume of use and impact adequate criteria for the selection of drugs for this list? And if the answer is yes, how should impact be defined? And if not, why not? And what additional factors should be considered?

And just to reiterate, Dr. Murphy has

already made the point, but we're not going to talk about individual drugs this afternoon. We're talking about the process of developing and maintaining these lists.

So would anybody like to comment on the issue of volume and impact being adequate criteria for selection of drugs? Dr. Fink.

DR. FINK: I guess I would take the negative to that and say that although they are good criteria, they were not sufficient in that -- and I think the list of drugs illustrates that -- there may be the situation which an off patent drug is replaced or is replaceable by a safer, newer drug that even carries a pediatric indication, and in that setting, even though the older drug may have volume and impact, it's not a very good one to push studying.

DR. MURPHY: So would we possibly use the criteria that there are numerous other options then?

DR. FINK: Yes.

DR. MURPHY: Okay.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I tend to agree with Dr.

Fink in great part, but I think volume still has to be a part of the recipe that we use to select them because it is true that use doesn't necessarily mean appropriate use, and we could all pick examples off of the list we saw a moment ago to illustrate that.

But it's a beginning, and then I think we are going to have to add the other criteria that we're going to discuss subsequently to try to flesh this out and probably come up with a weighted list of criteria that will give us a scoring tool to select the highest priority drugs.

But certainly utilization or volume utilized will have to be one of them. Impact to me is going to depend on how we define that. Impact economically, impact in terms of child health in that particular disease category.

For example, there's several beta agonists on the list that are probably used much, much less commonly than albuterol. Now, should we waste resources in studying those now even though they're off patent and have some use?

Cimetidine, there are much, much better H_2

blockers out there that have a lot fewer problems associated with them. Should we waste resources enrolling children in studies to study that even though it has some use?

Well, probably not, but we're going to have to have other criteria, but I think use is one of the criteria we'll have to include.

CHAIRPERSON CHESNEY: Dr. Gorman.

DR. GORMAN: I would like to add a suggestion of uniqueness to this list, and not to replace either volume or impact, but a drug that is uniquely indicated for disease whether it has a high therapeutic index or a low therapeutic index or is even considered to be very efficacious.

I would think of acyclovir when it first came out or perhaps one of the Alzheimer's drugs when they were the only mover in that field, that these drugs should take a place on the priority list.

CHAIRPERSON CHESNEY: Dr. Glode.

DR. GLODE: I should just introduce myself to the committee because I came late. I'm Mimi Glode. I'm pediatric infectious disease from the University

of Colorado.

I also agree that the starting point I think should be volume, but then I think the definition of impact should perhaps be enlarged because I would certainly agree with uniqueness, but I would also, after I looked a volume, I think I would look at the seriousness of the illness being treated, and then I would look at the therapeutic index of the drug.

So if I have a dangerous drug and a disease with low morbidity and mortality, that's a big issue to me. On the other hand, if I have a life threatening disease, you know, I again am willing to play things a little bit differently in terms of therapeutic index.

CHAIRPERSON CHESNEY: That could potentially come under impact if we define impact to include that.

DR. GLODE: Yes, yes.

CHAIRPERSON CHESNEY: Dr. Nelson and then Dr. Luban.

DR. NELSON: This reminds me of the