discussions that went on in Oregon about trying to triage health care.

(Laughter.)

DR. NELSON: Pardon the analogy, but there they linked a couple of things and came up with a list, and then they used buckets. It strikes me that impact -- I might define impact a little differently and actually include volume in the definition of impact and consider impact as a combination of volume, which is both use and disease. It's not only something that is used. It's also prevalence of a particular condition.

And then severity regardless of volume, and so you end up almost with a product. Something that's severe, of low volume would be equally ranked with something with volume and low severity.

And then you end up with what I would call adjusters, which uniqueness would be an adjuster. The existence of various alternatives or options would be an adjuster. The other adjusters would be existing information that exists much on the order of the original approach to labeling.

If you've got published information and the like, I assume that that will figure into the equation, and also the consequences of misinformation in the use.

The other thing that I might add is some of the drugs on there, someone working in the ICU, it just strikes me if you're titrating the physiologic effect. Maybe I'm ignorant in my use of some of those indications, but it's not clear to me I need a lot more efficacy data for dopamine in the ICU. I just titrate it up until I get an effect. If I don't, I switch to a different drug, and there are a lo of other ones that are available to me.

So I'm not sure I would use the usage there. I wouldn't put that very high compared to other things.

And then I thought I had one final thought, but it just went somewhere else. I'll stop.

DR. MURPHY: would you repeat your adjusters.

I'm sorry.

CHAIRPERSON CHESNEY: No, go ahead.

DR. MURPHY: He had a number of adjusters, and I didn't get them all. Limited options is one and consequences of misinformation.

DR. NELSON: Options or alternatives exist. Certainly if there's -- I'm not sure I would favor newer agents. If there's better agents, sometimes actually off-patent agents are, in fact, better than the newer ones or certainly no worse.

Existing information. I mean, in ways you would make decisions about issuing either a request for labeling. Those same kinds of considerations that might exist. Consequences of misinformation.

Oh, the other thought was I just want to point out that in this arena, the Best Pharmaceuticals Act states that negative studies are in the public arena, and I want to point that out because I think that's an important component here. If we end up with a negative study, then we know pediatricians will get that data.

CHAIRPERSON CHESNEY: Dr. Luban.

DR. LUBAN: I'd just like to ad another adjuster might be either adult or animal data that

suggests adverse effect, and those kinds of drugs would be additional drugs to have special attention paid to them.

CHAIRPERSON CHESNEY: Dr. Spielberg and then Dr. Ebert.

DR. SPIELBERG: Following up on what Skip said, in terms of available data, I think it should be looked at both from the point of view of efficacy, you know, is there a huge literature out there demonstrating efficacy, but also on the safety side, and that comes both from published as well as AE reporting.

Is there an identified issue out there? You know, if it ain't broke, it may not need to be fixed., If it is broke, it should be fixed very quickly.

And for many of these compounds, there's already a fair amount of information out there, some of it good, some of it bad, but I think we're going to have to evaluate all of it in terms of setting priorities.

The other thing that hasn't been

discussed, and this is putting on my ICH hat, there is discussion, as we'll see, in Europe now going on about similar issues with respect to off-patent medicines that are widely used in other venues than the United States.

And one of the things that I think we should be thinking about both from the practicality of doing studies internationally, sharing data around the world for all sick kids around the world, is think at least in part about the international impact of compounds.

This might be in part through the WHO essential drug list if there are drugs on that list that also appear on our list and also appear on the European list, it may provide us an opportunity for working together, getting the data more rapidly, and using it for labeling in all venues as well.

So although this is a U.S. initiative, I think since we already have participated in the ICH process, in order to make that really a live process for kids around the world, I'd really like us to consider international need as well.

CHAIRPERSON CHESNEY: Yes?

DR. ST. RAYMOND: I'm Dr. St. Raymond from the European Medicine Agency.

And we had a similar discussion in our agency concerning the priorities and the needs. So it's interesting to hear you discuss because we have the same criteria at the beginning, discussing indications, severity, the use and the volume.

But for the volume, I just have a restriction that it is also related to frequency of the disease. So a drug of very little value, but very frequently prescribed, I don't want to be difficult. Auralgan, for example, may not be for me a priority because ear pain can be treated by other means, and otitis media is certainly a big problem. Ear pain is something different.

So we have this discussion. We have also discussed the needs as expressed by the pediatricians and the considered reserves from lone societies, and the first one that came up was pain and pain treatment. Therefore, we looked at whether we had a pain treatment available for all types and all

severities of pain in children and for all age groups, and that's how we identify some age groups and some levels of pain treatment that were still needed, and that's where we, for example, started some studies of kinetics of codeine in less than one year olds.

And the last point that was interesting for us was considering what was said earlier that there has been a lot of published data, sparse sometimes, but sometimes available and sometimes of good quality.

It would be also a good thing to look at the fast winners, where you just need a little additional data to get a full picture of the drug rather than starting from scratch for a drug from which you know nothing.

I support also the need for new treatments rather than necessary, although we know a lot about the safety of all the drugs as compared to new drugs.

CHAIRPERSON CHESNEY: So symptoms also could come under the category of impact, where I've got pain as well.

Let's see. Dr. Ebert, you had a question?

DR. EBERT: Well, I'm not sure I have much to add to what the previous two speakers stated so eloquently, but I was going to mention that, again, I think that the volume while it is important is somewhat insensitive as a measure.

It occurs to me that medications that are used frequently may be used because they are quite efficacious, but we know little about their adverse effect profit, or they may be used frequently because they are quite efficacious, but we know a little about their adverse effect profile or they may be used very frequently because they are very safe, but we have some questions about their efficacy.

And so certainly I think the impact issue is the one of most interest to me.

CHAIRPERSON CHESNEY: Dr. Nelson.

DR. NELSON: A question for Steve.

Would you carry your desire for international approach to this to look at volume and severity diseases, things that aren't that prevalent within the United States? How far would you go with that assessment?

DR. SPIELBERG: In the best of all possible worlds, for sure, although there are obviously diseases that afflict the vast majority of children that outstrip anything that we have here in terms of diseases by many orders of magnitude, but some of the drugs aren't even available here, are labeled here.

So that it may make it hard from the agency's point of view in terms of those compounds. You know, I mean, when you put out numbers like two and a half million children still die of diarrhea every year around the world despite availability of oral rehydration solutions, we've got problems out there. All of the worms, all of the other infestations, all the other infectious diseases which we rare see here.

On the other hand, I would argue passionately about the smallness of the world right now. We are all very much interdependent. Toronto was interesting in that regard. I spent 11 years in Toronto with a huge immigrant population. I saw all the diseases that you see everywhere else on earth and

didn't recognize them until I had seen one of them.

We all are, indeed, subject to similar kinds of things, but obviously we still have to take into account it's the U.S. congressional, as well as an FDA initiative, but I'd love to see some blend of that to be able to do some of those things.

DR. NELSON: I mean, to the extent that there may well be researchers interested in those questions that are local, but yet the population served would be international.

DR. SPIELBERG: Yeah.

DR. NELSON: In many ways this list will establish RFPs and the like that perhaps having some portion of it designated so those local researchers at least have something to apply to, that would be interested in international diseases.

DR. SPIELBERG: No, I agree, Skip, and I think it's in all of our interests as human beings. It's in al of our interest health care wise. It's in all of our interest in term so world peace to decrease devastation of disease, which is going to lead to conflict.

So I think to the extent we can use such a mechanism and where it can be skillfully and cleverly applied, looking through WHO needs and looking through our needs, looking through European needs, I'd love to see it happen, indeed. I think we should try it.

CHAIRPERSON CHESNEY: Dr. Fink.

DR. FINK: Yeah, the only concern I guess I have, I agree in theory with the idea of internationalizing this where possible, but I also see a major problem there that the international needs and sometimes criteria by which success is judged are so entirely different from the way they are judged in the United States.

Dr. Gorman was just advising m that rotrovirus vaccine in Third World countries will save thousands of lives, even though it's unacceptable in the United States because of a minor incidence of Ennis susception (phonetic).

So I think some of the international studies would be very difficult because we're really looking at totally different populations and a totally different background in which we are performing the

studies.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I just wanted to come back to something that Skip said a moment ago because he reminded me of another adjuster maybe we could call it, and that is I agree with him that the pressers, dopamine and doputamine -- he doesn't need labeling because he's an experienced intensivist working in a premier pediatric institution, but the general surgeon in a community hospital, the general pediatrician or the adult ER doc in a community hospital who's taking care of the six, eight, ten year old doesn't have that skill, doesn't have that knowledge.

And when they go to look up information about dopamine or dobutamine today, it says, "No information available under 12 years of age." So it doesn't help them at all.

I think for some drugs, and these are probably two good examples, and we could pick a lot of others, the labeling is probably going to be much more important for certain areas of practice than it will be in the subspecialty areas of practice, and we're

going to have to take that into consideration probably drug by drug.

CHAIRPERSON CHESNEY: Dr. Murphy, have we addressed the impact volume issue? I think what I hear people saying is that impact is the most important issue, and to include in that volume of use, volume of disease, disease severity, the options and alternatives.

Dr. Luban mentioned adult and animal data that indicated significant adverse effects, symptoms, including pain, as something that would have impact, and then diseases with worldwide impact.

DR. MURPHY: Of those adjusters that you just listed then, when you list a positive, then the flip side of it is a negative, if you will. So when we are looking at this, if there are no negative effects in animals, I just want to make sure. Then that would be a positive versus clearly the negative that could be then counterbalanced by one of these other adjusters, the severity of the disease, the other information that's known or not known sort of approach, but trying to think of all of those and how

one could end up having a ranking with it.

They're equal is what I'm trying to say. You're considering all of those as equal phenomena.

CHAIRPERSON CHESNEY: Would we like to rank any of the adjusters under impact?

I can read them out again: volume of use, volume of disease, disease severity, availability of alternatives, adult and animal adverse event data that would indicate looking at it more carefully in children, symptoms, and worldwide disease distribution.

DR. SPIELBERG: We left off availability of data.

CHAIRPERSON CHESNEY: Availability of data. Sorry.

DR. SPIELBERG: Yeah, human data, both --

CHAIRPERSON CHESNEY: Thank you.

DR. SPIELBERG: -- efficacy as well as safety data.

DR. FINK: I think we left off a negative, that if there are safer, effective alternatives.

CHAIRPERSON CHESNEY: If there are safer,

effective --

DR. FINK: Alternatives, that that actually would be a negative adjuster.

CHAIRPERSON CHESNEY: Okay. Anybody want to hazard a prioritization? Dr. Danford.

DR. DANFORD: I won't volunteer to put those in order, but I thought of one more that maybe we should add to the list, and that is the likelihood that an appropriate state can be designed to answer the question.

And I think back to our discussions of this morning where we had such a difficult time thinking of how we would study the proton pump inhibitors. I would suppose that pharmacologic agents that were out there for conditions in which the patients had such a degree of confounding conditions and poorly designed processes that we were treating would probably fall pretty low on our list of things we would like to investigate and those conditions that are well defined with good endpoints for treatment that could be easily studied with the idea that we would get valuable information when we were done ought

to be higher priority.

CHAIRPERSON CHESNEY: So that would be a negative adjuster, the ability to design experiments to get the answer.

Let's see. Dr. Ebert, I think, was next and then Dr. Nelson.

DR. EBERT: Well, again, just potentially one other additional adjuster might be some issues of economics. I would assume that many of these agents being off label are reasonably inexpensive agents, and clearly there are some circumstances where more expensive compounds do have an advantage, but I would assume that in some cases that if one starts to look at cost effectiveness or cost benefit, that that could also weigh into the issue here.

DR. MURPHY: I'd like to say two things. I don't think the agency is going to do that. Okay? That's number one.

And, number two, I guess I have a problem with -- and I'd just like further discussion because Anne and I were getting in a sidebar conversation here about saying that because it's difficult to study or

we're not quite sure, that that drug not be on the list because, number one, how do you know?

I mean, think about all of the work and the effort we've gone through with the GI drugs trying to figure out how to study them, and, yes, it's difficult, but I mean, I'm not sure whether we want to say that ought to be the criteria or two would be maybe that is an additional way to motivate because I think what somebody has already mentioned is that the products getting on this list will be -- it doesn't mean that we will ask for a written request because that's what all of these criteria are, but it does mean that there is a higher potential that they might move forward and have an RFP put out for them.

And so that approach could incorporate maybe the questions that we need answered before you actually went to the next couple of steps. So I'd just like to hear some more discussion about difficulty in designing the trial as a criteria to decide whether you would put something on a list or not.

CHAIRPERSON CHESNEY: Dr. Fink?

DR. FINK: No, I --

CHAIRPERSON CHESNEY: I'm sorry.

DR. FINK: Well, my comment was actually not related to designing the trials, but I would be, I guess concerned that as we try and rank order this list we've got a lot of volume criteria there, and if we stick to that and we let volume criteria, volume of usage, volume of disease be heavily weighted, we're going to keep orphan diseases orphan diseases on our own list.

So I think uniqueness of the drug has to be weighted very heavily to compensate for the volume issues, which are obvious, but could kind of push everything else to below the threshold.

CHAIRPERSON CHESNEY: So uniqueness of the agent.

DR. FINK: Yes.

CHAIRPERSON CHESNEY: And, Dr. Nelson, I'm sorry I didn't get back to you before.

DR. NELSON: No, that actually was similar to what I was going to say. One could take this list, which you say had a list of X number of drugs, 25, 30,

whatever, and then decide that there's certain subsets that fall into different categories, and it's the subsets themselves as opposed to the individual drugs that would be felt to be of higher priority.

So, for example, you could take those out that would be in situations where there are few other therapeutic alternatives available to that population of children and say that is the class which we would consider more highly than researching another class, since you don't know exactly how much money you're going to have to give.

I mean, I believe was it anywhere from two to three million to eight million that it cost to do a single study that's a PK/PD or something, Steve, something along those lines, or ten million?

DR. SPIELBERG: It's going to be very compound dependent. For drugs where we know a lot already and there is, you know, missing data and such, it could be very expensive. If the data are out there are viewed as totally inadequate and you have to start from scratch, then you're talking very large programs.

DR. NELSON: Well, basically with $200

million --

DR. SPIELBERG: But I mean, if we need some PK/PD, we can do it very inexpensively. If it's going to be, you know, a ten-year follow-up study for safety issues, you're talking enormous amounts of money. Again, you know.

DR. NELSON: Well, thinking about triaging the amount of money, you know, basically you want to have some way of differentiating on that list because there may be a need to make distinctions between competing drugs in the absence of sufficient resources to support both studies.

DR. SPIELBERG: I mean, for example, I think the issue that Ralph brought up with dopamine and, you know, folks not like you having to use dopamine, obviously, you know, I ran a quick Medline on dopamine. There are hundreds of publications on dopamine which, if, I imagine, put together with those pieces of missing data, could very readily lead to labeling under a combination of, you know, send us everything under the '94 rule because this is what's missing. Let's fill that in and get it labeled for

anyone who might be faced with a child in an emergent situation.

So for relatively little investment, you might get really major return in terms of children. So I think that kind of thinking would be helpful in terms of priority because you want to think what the labeling is going to do ultimately.

You know, if it was only a drug used, say, in cancer chemotherapy by Victor, would it matter terribly much whether that information is in the label if all children are treated at, you know, COG centers, as opposed to the scenario that Ralph described of, you know, a child coming in in shock to an emergency room in a small town and there's just no pediatrician or pediatric pharmacists or reference books. All there is is the PDR, and the label may be life saving.

And those things could be done relatively inexpensively with relatively quick turnaround because there's already a lot of data out there.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I think Dr. Murphy's question a moment ago is very important, and if I

understood you correctly, you were getting at the point we might have a drug that we think is pretty important and it meets all of these other criteria, but there's no way we're going to be able to study that drug for various reasons.

And one reason is an old drug that's in common use and everybody thinks they know how to use it, it's almost impossible to enroll into a study because people just don't want to do it. The physicians don't want to, the parents don't want to. It's hard to justify it.

So we will find situations, I'm sure, where all other reasons point to maybe putting that drug as a relatively high priority, but when you really think through it, it's going to be impractical to do it, and we're going to have to be sensitive and be realistic about that in some situations.

CHAIRPERSON CHESNEY: Any other -- oh, Dr. Gorman.

DR. GORMAN: Following up on that, it struck me as very prophetic that the '94 list and the 2002 list had a lot of overlap as far as agents, some

of which I think the people around this table would think have very little clinical usefulness.

And I think the answer to Dr. Murphy's question is not that these agents should not be on the list, but it will determine their duration on the list in the sense that it's difficult to do studies. There may be a good reason for them to be on the list, but they'll never get off the priority list.

CHAIRPERSON CHESNEY: Dr. Glode.

DR. GLODE: But, again, I think back to the issue of some of the drugs on this list are not candidates for safety and efficacy study, i.e., ampicillin from birth to one month of age. I mean, you're not going to do a placebo controlled trial of IV ampicillin for Group B strep. meningitis, I hope.

So what's missing there? Maybe just a little bit of PK/PD data is all that's missing. Ampicillin, I think its safety record in the pediatric populations, as well as adult populations, and its efficacy track record; so you could get that labeling, it seems to me, very easily. There's just a little bit of pharmacologic information missing and then that

would come off that list.

So it's on the list for a volume reason, but it's not on the list for the other reasons.

CHAIRPERSON CHESNEY: Are there any other comments specifically to Dr. Murphy's question about whether the ability to design studies such as we went through this morning should automatically relegate a drug to a lower position on the list? Any other comments about that?

Anybody disagree with that statement? I think Dr. Kauffman already raised one situation.

Dr. Nelson.

DR. NELSON: There really hasn't been much conversation about process, but presumably there will be a study section of some kind that will be evaluating the proposals, and I would anticipate that it would make sense for the feasibility to be dealt with by that group rather than be dealt with on the list.

I mean, they're going to look and say this is bad science. It's not going to answer the question, and then that's not going to be funded. I

mean, it's as simple as that.

DR. MURPHY: And the process could involve, you know, reporting back to that effect.

CHAIRPERSON CHESNEY: Do you want anymore input on the criteria issue or should we move on to the process issue?

DR. ROBERTS: One area that has not been addressed for developing products that go on the list and which actually Congress asked us to look at is the question of what if a reformulation is necessary to study the product in the pediatric population. Who is going to do the reformulation? And what are we going to use for the studies?

CHAIRPERSON CHESNEY: Dr. Spielberg.

DR. SPIELBERG: That's, again, coming back to my old theme that formulation is the heart of pediatric therapeutics. It truly is.

Having struggled now on my side of the fence over making formulations, doing stability, "oops, it turned brown in four months," "oh, it crystallized out," "oh, we have an excipient that isn't acceptable in Europe and is here, and we've got

to get" -- you know, clearly, the only way we're going to get standardized formulations is from a sponsor who is willing to do all of the CMC work under GMP regs., get the stuff studied for stability.

But if you think about it, that's absolutely necessary for afterwards because who is going to distribute it and who is going to be responsible for its availabilities.

You know, my 14 year old couldn't get a tetanus shot yesterday because the pediatrician didn't have it. That's pretty sobering, I must admit, very upsetting to us.

But you know, availability is entirely dependent on a supplier having that on the shelf and making it and, you know, if there's a change in GMP and having the inspectors out and doing all of the things that we normally do.

So if we do need a formulation, somehow we have to come up with sponsors, and I suppose it could be almost anyone. It doesn't have to be the originator. Sometimes it could be a small operation like Ascent Pharmaceuticals that has developed several

pediatric formulations.

Sometimes it may be a larger sponsor who is looking for a compound to fit into another portfolio, but recognizing you'll only get, you know, what, three years Hatch-Waxman for the formulation. You know, I've spent sometimes as much on formulation as I've done on clinical trials. And so the incentive is low.

But it's something really that I don't think was thought through in terms of the legislation that we really do need. Otherwise we're going to fall back into the old the pharmacist makes it up extemporaneous formulation. Is it validated; isn't it validated, et cetera?

So I think it's a real quandary, and unless you can find somebody who's willing to take it on and do all of the things necessary under GMP to produce a marketable formulation and distribute that formulation and make sure it's available, we've got a problem.

DR. MURPHY: And I think what Steve is describing is you would have to write this whole

process, the request and the RFP to somehow say you're going to now manufacture and continue distribution, and I think if you think about that for a little while, there would have to be a lot of money to do that.

DR. SPIELBERG: Yeah, even just to recover the cost of doing the CMC and stability and all of the other things that we normally do. Certainly NIH can't be in the business of making and marketing drugs. That's not their job.

The academic centers really can't either. It has to be some manufacturing process, and again, it doesn't necessarily have to be the sponsor. It could be a generic; it could be almost anybody, but you're going to have to find a champion who's going to be willing to do it.

And if you think about it, you know, I assume for the dopamines and dobutamines for the world, they're IV. There are formulations that are already used. We're going to be okay.

But there are certainly going to be products where that's going to be an issue, and I

think it would be very unfortunate to go back to one of the old compounds and start recommending crushing and giving a tenth of a tablet. If we do that, I mean, we've just gone back 50 years. So we don't want to get into that scenario.

And if no sponsor can be found, it may end up being an exclusionary issue. It may fall off the list because something is needed and you can't find anybody to do it, but I think before giving up, I'd beat the bushes, you know, to the Ascents and everybody else, and see if it might be in their interest to pick it up if, in fact, the data are generated under quality studies done by or through an NIH mechanism.

CHAIRPERSON CHESNEY: Would a new formulation have a patent or, I mean, would they be the only people who could market it for a period of time? I mean, would that be an incentive to do it?

DR. SPIELBERG: I mean, what is it, typically three years? And with pediatric sales, you might never be able to recover the cost of R&D and manufacturing. You might be at a loss situation, in

fact.

But that is a real issue, and it's one that's worried me and, I know, worried you guys, too about how to do it, and all I can think of is hopefully some of the smaller companies might find it in their interest to develop a portfolio.

You'd never do it with a single compound, but if you had a technology that might be able to do several compounds, even then, I mean, each one is looked at separately for GNP and standards and, you know.

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

DR. NELSON: Well, Steve, just to educate me, are you able to at least give a ballpark estimate if you had to develop a new formulation to what the range of cost might be to do that? I mean, are we in the two million range, the ten million range, the 500,000? I mean, where are we talking, out of curiosity?

DR. SPIELBERG: Millions, but all over the place depending on difficulty. You know, I was on one

program in a previously life at a previous company that had the first protease inhibitor available. We spent three and a half years unsuccessfully trying to develop a pediatric formulation and spent a fortune bringing in every expert around the world that we could, but the stuff was a rock and couldn't be done.

DR. NELSON: Well, there's going to be outliers, but I guess the question would be could you include --

DR. SPIELBERG: It's going to be millions, and then you've got manufacturing costs, you know. Can it be unit dosed? And then you've got vial costs, and those things I don't even know what it costs to do those things.

DR. NELSON: Well, as a general impression, if you had the up front formulation cost as part of the grant, if you will, would a manufacturing sponsor be able to support the marketing and distribution costs out of the cost of the drug once it's developed and tested so that at least it will sustain itself?

DR. SPIELBERG: Right. I see what you're

saying, yeah. I don't know enough on that side of the business. We'd have to get some input from the CMC folks to know if that's even feasible, and again, I guess it would vary a lot.

I mean, if you can provide 50 mL bottles of the stuff, no problem. If you have to unit dose it, very expensive. If it can't be done as a syrup, it has to be done as a chewable tab or a blister pack or whatever. Each of those things dramatically increases the cost.

So I think it will be a case by case basis, but I mean, that's something to consider, but I don't know if Congress envisaged funding formulation development because it would have to be done by a sponsor that has GMP standards and FDA, you know, qualified labs.

DR. ROBERTS: Actually, the act only talks about formulation in two places. One is that it should be considered in developing and prioritizing the list, and then once the third party does the study, when they report back, if they feel that a formulation is necessary for the product, then that

should be part of their report.

And then we are supposed to send a letter to the sponsor about the product and say --

DR. SPIELBERG: But you see, that would require additional clinical studies on the formulation.

DR. ROBERTS: -- a formulation has been recommended that you did.

DR. SPIELBERG: But then you need both formulation and clinical studies on the formulation, at least bioequivalents in adults or --

DR. ROBERTS: Yeah, you'll need that.

DR. SPIELBERG: Which isn't a lot compared to the cost of the formulation development, but it is cost.

DR. O'FALLON: It seems to me we've got two different things going on here. One of them is an issue of need for treatments for certain things, and the second issue is the cost of doing business, of trying to do the studies, and they may be feasibility studies, such as issues such as we were talking about this morning. They may be financial issues, such as

the formulation issues.

But it seems to me that there are a couple of things going on here. First, we should be advising the FDA on how to identify or prioritize -- what would you say? -- areas that need to have treatments for children.

And then after that, they can go about the sub-prioritization based on some of these other feasibility issues.

CHAIRPERSON CHESNEY: Any other issues like formulation, Dr. Roberts?

DR. SPIELBERG: The only other thing to mention under formulation, if, indeed, we're to keep costs down, the clinical studies should be done with the formulation that's going to be used or you're going to have to repeat it all, or at least repeat the PK and bioavailability and bioequivalent stuff, and you for sure don't want to do that.

And the other thing is if, indeed, the need is the small babes and the only thing available is a 75 milligram tablet and the estimated dose in those small babes is going to be, you know, eight, you

know, a milligram per kilogram or something like that, you can't do it until you have that formulation. You're absolutely stuck. You can't go forward.

And if we did with extemporaneous formulations, I think that really would be a negative for all of us to go back to the bad old days and do that.

DR. KAUFFMAN: Question. I have a question for the FDA folks. Is there -- do you think there's the option under the act that you could separately bid the formulation apart from the study contract? In other words, so that a CRO could pick up the study part, but you would contract for the formulation with a company that had all of the infrastructure and expertise to do that rather than one entity having to pick up the whole thing?

And would the public funds pay for formulation, pay that cost?

DR. ROBERTS: Well, this is really not an area that we have discussed. It sounds like since clearly the third party who does the studies is support to report back as to whether they feel a

formulation should be made, and then the agency is to issue some kind of letter to the sponsor who makes the product that it's been recommended that a formulation be made. There's no requirement.

Congress was seen -- I don't know what they thought we were going to use for the studies is my problem.

(Laughter.)

DR. KAUFFMAN: It's a big hole in the hat.

DR. ROBERTS: Yeah, it really is.

DR. MURPHY: And I think actually what we're trying to say is that certainly where we have formulations that are already available, that we could then do the studies by appropriate mechanisms because if we have to make a new one, we will.

Where we don't, I don't think we're in the situation where we have to say, well, we can't do anything. I mean, I know, Steve, none of us want to go backwards, but sometimes maybe the initial step is to develop the studies in whatever solution that you may have to develop and then study that for stability and see then the second process that Rosemary is

mentioning would be the way you would go.

There would still have to be those studies that aren't that hard. I mean, you know, the stability and the bioavailability, I mean, those things we could do. So I think --

DR. SPIELBERG: Those are relatively inexpensive compared to the rest of the problems.

DR. MURPHY: This whole formulation issue, I think we clearly are not quite clear how we're going to implement it at this point. When we get to the first situation where we, you know, are going to not have a formulation, we're going to have to look at, you know, a lot of things like the possibility of doing other approaches, carving out parts of it.

And I think for right now it was important for Rosemary to put it on the table that we have to look at that, but that's been an issue, as you all know for written requests and for the rule, both, where, you know, we can ask for it, but it doesn't mean we always get it.

DR. SPIELBERG: Just one final thought on it because I am sitting next to my international

colleagues. Most kids in the world don't have refrigerators, when we're thinking about international formulations, and I remind our chemists of this all the time because we have one situation where we have this great liquid, but when it's put out into a truck and transported, it degrades unless you have a refrigerated truck.

Well, that's fine here, but it really isn't fine in most of the world, and that's really a challenge that I have to keep reminding myself of and my colleagues in industry, that if we are, in fact, to treat kids around the world, we need formulations that can be used around the world.

DR. MURPHY: I think our colleagues from Europe are going to hit you on the head with a refrigerator, but --

(Laughter.)

DR. MURPHY: -- they didn't know they were lacking them.

DR. SPIELBERG: In Europe, but they're frigid. They're small. So there's no room for the medicine.

CHAIRPERSON CHESNEY: Thank you, thank you.

I think the process is much easier. Comments about -- let's see. Maybe we could have the second question.

Dr. Willoughby and Dr. Murphy and Dr. Roberts have described a process that includes use of databases, professional organizations, and an expert panel or panels. Are there other sources that the FDA and NIH should consider in the development of the list? And how should the sources be weighted?

And Section B, how can the committee make their recommendations happen in a timely fashion? And what information would be important in reporting on the progress?

So let's start with the first part, which is: are there other sources? And if I could make a comment to that, I think Dr. Kauffman mentioned the dopamine issue for the small community hospital where there was nobody available that knew anything about dopamine.

And I wondered if we couldn't also include

such professional organizations as emergency room physicians, family practitioners, nurse clinicians. There are many nurse clinicians out there who are in primary care practice who don't have ready access to physicians all the time.

And then if I could also just suggest that all of the subspecialty organizations be required on some kind of annual basis to put this on their agenda and review what's happened in the previous year and be expected to get their recommendations to you in a timely fashion, but those are my comments.

Others?

DR. SPIELBERG: And not to forget AAP. I assume that was assumed, but the AAP is key in coordinating all of that.

CHAIRPERSON CHESNEY: That's sort of a given.

DR. SPIELBERG: Yeah.

CHAIRPERSON CHESNEY: So lots of other suggestions here.

Dr. Luban and then Dr. Glode and then Dr. Nelson.

DR. LUBAN: Well, one group that we didn't discuss at all is fetal medicine, and I'm not sure how much applicability we have with at least what's on the priority list now, but should that list change, I think we need ACOG representation in any kind of review, particularly if we're dealing with any kind of fetal medicine.

CHAIRPERSON CHESNEY: Excellent suggestion in terms of intrapartum HIV drugs, intrapartum Group B strep drugs, among others.

Dr. Glode.

DR. GLODE: I'd just like to second your suggestion that subspecialty organizations be addressed because I think the subspecialty organizations working with just a smaller database of their own medications that they are familiar with can kind of synthesize the issues about impact from their experience would be very good.

I wondered about if there's a list of approved orphan drugs under the Orphan Drug Act or something and someone has gone down that list and looked at the relevance of those drugs to the

pediatric population and, again, seen if any of those would be important to look at.

CHAIRPERSON CHESNEY: Dr. Nelson.

DR. NELSON: I think that what I'm going to suggest may be implicit in some of the areas, such as the FDA internal process and how individuals on the expert panels might go through their work, but I would want to make explicit sort of an evidence based evaluation of the literature and what exists and the like, you know, using sort of a formal analytical approaches, papers, that sort of thing rather than just a bunch of experts saying, "Well, I do it this way."

We assume it's literature based when an expert says that, but I would want to make that explicit instead of implicit.

CHAIRPERSON CHESNEY: Can I add one more comment to what I said? When I talked about emergency room physicians, I don't think that -- I mean, we need pediatric ER physicians, but particularly adult ER physicians who are doing a lot of the pediatric care in the community.

And in small, backward communities like Memphis, one of our major teaching hospitals uses adult ER physicians to oversee the care of children. So I'd like to be sure that we don't just include pediatric specialists, but generally ER physicians.

Dr. O'Fallon.

DR. O'FALLON: I'd just like to follow up on what Dr. Nelson said, but extend it. Remember databases are only as good as the data or the studies or whatever they came from. So if you're going to be trying to put together databases, and I do think that's a great idea, I think they also need to be evaluated, that is, the strength of the evidence, the quality of the study to produce the data needs to be evaluated, and that information needs to be involved in the database so that you're going to be able to tell whether it was anecdotal case history stuff or whether it's, you know, a highly well done clinical trial or anything in between.

CHAIRPERSON CHESNEY: Dr. Fink and Dr. Kauffman.

DR. MURPHY: Could I just say one thing?

I do want to just reinforce that within each of the divisions in these products are physicians who have tremendous technical expertise and do read all of the literature they can get their hand on before they even move forward down this list.

So I do want to reinforce that that is a process that's already occurring. So it always warrants reemphasizing, but it does occur as part of this process.

DR. O'FALLON: Is it published? Is it available to the one who reads it?

DR. MURPHY: Do our medical officers publish their reviews? Yes, we put them up on the Web.

Do they get them in the medical literature? Yes, occasionally, but again, often because their reviews are initiated because of an application, it is in response to a study that has been done by others.

And so unless there is some sort of cooperative agreement that there's an issue that would not cause a conflict of interest for FDA, they would

not be publishing on that specific area.

CHAIRPERSON CHESNEY: I have Drs. Fink, Kauffman, Rodriguez and Chesney.

DR. FINK: Just to the groups that should be included, I guess, I'm not sure what the proper terminology would be, but to some degree orphan disease associations that are too small to have reached the mantra of professional organization. Because if we exclude them from this process, they're going to probably go directly to Congress, which would really bypass the process and make it worse.

CHAIRPERSON CHESNEY: Are you thinking of disease other than what Dr. Glode was -- she was talking about the list of orphan drugs.

DR. FINK: Yeah, I mean, the neurofibromatosis association. There are a lot of them out there, and they need to have some option for input or at least to state their case. They shouldn't be weighed as highly.

CHAIRPERSON CHESNEY: Oh, okay. Subspecialty groups. I'm sorry. I misunderstood the list versus the subspecialty groups, and that would

include like the group that we've heard from today.

DR. FINK: Right, but obviously I think you want to let all groups that want to have a voice have a voice not just --

CHAIRPERSON CHESNEY: Yes. Thank you. I appreciate that. I misunderstood.

DR. LUBAN: Dr. Chesney, if I could just add, there is a national organization of rare diseases which exists and has broad based representation for orphan diseases, and that would be an excellent group.

CHAIRPERSON CHESNEY: Dr. Murphy, you got that? I didn't know about that.

DR. MURPHY: Yes.

CHAIRPERSON CHESNEY: Okay. Dr. Kauffman.

DR. KAUFFMAN: I was just going to suggest the USP has been maintaining evidence based database on pediatric indications and dosages and so forth for years, and that database is a wealth of information. It's not the sole source of information by a long shot, but it has a lot to add to this and to borrow from.

So I would suggest we work with the USP on

this also.

CHAIRPERSON CHESNEY: Dr. Rodriguez.

DR. RODRIGUEZ: It's interesting. We're thinking in the same lane. They had provided a list of drugs where there was a need for information. There was also a -- I'm talking about U.S. Pharmacopeia -- narrow spectrum, low spectrum, et cetera. I mean a wide spectrum, et cetera, et cetera, all that information.

It's interesting. Eleven of the 19 drugs that we actually flashed there were actually in their list independently developed, which in terms of going at it from a different way, we never touched bases until somebody publishes the list.

CHAIRPERSON CHESNEY: I had just two other suggestions. One is the otolaryngologists who treat probably more otitis media than the pediatricians, and the other is the child psychiatry organizations which we heard about today. I think that's a very, very important group to include, and we've already discussed issues in this committee relative to that.

Dr. Santana.

DR. SANTANA: And this may be like a restatement of a fact that's so logical it shouldn't be restated, but to pay attention to what the European colleagues are doing because if they have a similar list with similar studies, we shouldn't be expending our resources on duplicating something that's going to be so logical in terms of adapting it to the U.S. population.

CHAIRPERSON CHESNEY: Do you need more ideas?

DR. MURPHY: The process as we see it right now would be that we would look at various needs. We have a product that's on the list. We develop a written request for it. We send it to the sponsor.

The sponsor says, "I don't want to do it."

We work with our NIH colleagues to turn it into an RFP, and then there would be a section study involved with reviewing the RFP. At that point studies hopefully will be done, and then that information will come back.

Is there anyplace in that process that

this committee wishes to provide further input I guess would be one of the questions we have for you.

CHAIRPERSON CHESNEY: So the decision would have already been made that this was a high priority drug in terms of being studied, to go through this whole process? That decision would have been made right up front; is that -- go ahead.

DR. NELSON: I would think that in thinking about limited resources and triage, if you're sending out written requests, say, on 15 drugs that all fall into somewhat different classes, and then let's say the sponsors all say, "No, thank you," I would think that a study section would have an easier time evaluating that if they're seeing them grouped to where if you've got limited resources you're looking at Proposal A versus Proposal B versus proposal C.

So I guess it just raises a question about the timing of the process, that if it's going out sort of one by one by one by one, you might just run out of money when you finally see something that you would have wanted to fund, whereas you had funded something earlier that you might have decided would have been a

lower priority

So some thought about how you look at it all together when they come in, I think, needs to be considered, unless they give you all the money you want and it's not a scarce resource.

DR. SANTANA: Or unless all of the requests are made at the same time from the FDA perspective.

DR. NELSON: Well, if they go out at the same time and come back at the same time, they can, but I can't imagine you're going to be able to produce 15 written requests all at the same time, but maybe you can, but I doubt it.

CHAIRPERSON CHESNEY: Any responses to Dr. Murphy's question about what the role of this committee might be?

We've made lots of suggestions of other people and other organizations that could provide input, but what might our role be?

DR. LUBAN: I was actually going to reflect on what Skip mentioned. I think you can probably draw a parallel to a standard study section

at the NIH, where you attempted to let them all out at once with deadlines so that they all came back and your study section group or the equivalent of counsel would assist you in prioritizing them after they've been reviewed, but before they were let.

So, you know, it's exactly a similar parallel to what happens with NIH, and then we could serve or some fraction of us or some of us with individual added expertise could serve as a counsel.

CHAIRPERSON CHESNEY: A good suggestion. Any other suggestions?

Dr. Glode.

DR. GLODE: I was just wondering whether it would be worthwhile commenting on, as we have now suggested, all of these other organizations. One of the issues that comes up, do you just ask these other organizations to develop their own list and check it against your list or do you, in fact, send out the current list and say, "Now open for comment. You know, please comment and if you see missing items that should be on here," might be an easier process since you've already gone through lots of organizations to

get to this current list?

CHAIRPERSON CHESNEY: Well, we probably all have thoughts about that.

Dr. Nelson.

DR. NELSON: I think if you are going to send it out for comment you should make explicit the ways in which the list was developed, the kinds of criteria we've talked about, the various categories, and basically ask the individuals commenting to specifically address how their recommendations do or do not meet those criteria. Because otherwise you will just end up with people advocating, as they should, for their own particular interest.

CHAIRPERSON CHESNEY: My thought would be that the organizations had each year to indicate whether they had new drugs that they wanted to be considered or added and why they fulfilled the criteria.

I'm not saying when the first list came out. I happened to have been on the Committee on Infectious Disease at the time, and it was just overwhelming, and we really just couldn't even deal

with it, and it's a much different list now.

But I think if you had asked us what drugs do you think need to be better studied, and so on, we would have been able to cope with it better than we were being given a list and then asked to address issues on the list, if that makes any sense.

Mimi.

DR. GLODE: But was that list for 500 that you were looking at? I think it's different because what's missing from these 19.

CHAIRPERSON CHESNEY: Right. No, I agree with that, but I think if you independently ask a group of emergency room physicians what are the five drugs that you find yourself most often frustrated because you don't have good pediatric data, instead of saying to them, "Here are the ten that we think you might be interested in," I think if we could make them take the initiative to tell the agency what they need help with. Just a thought.

You had asked, I think, in here about committee recommendations for facilitating timely input. Any suggestions? Timely input from all of

these organizations with respect to how the list is developed. Any ideas?

DR. MURPHY: Well, I should mention to this committee, as you know, you're going to learn tomorrow you're now going to be scheduled to meet is it quarterly, Rosemary? Three times a year. So it may be a moot question, but just if we have an appeals process, that will be brought to this committee. So when you think about is there any additional input you'd like to have as far as we get input from other groups and we are producing additions to the list or taking this off of the list, we could present it to you annually or we could present it, you know, as an issue if there's an issue, or we simply -- well, I think those are sort of the two options, present it to you annually or present it because there's an issue about whether we would want to move forward with some of the criteria that you suggested and we're sort of stuck.

We don't want to add 50 more drugs, and does the committee have any other suggestions as to, you know, how they would use their criteria that they

have suggested and apply to those 50 more drugs that we've gotten that people want, that we can identify had missing information, and we have the utilization data, et cetera. Is there any role that you would think you would play in that, or do you want to just wait and see how we work through the study section issues?

I mean those are all options.

CHAIRPERSON CHESNEY: I saw a couple of hands here. Dr. Fink, did you? You didn't.

Dr. Santana.

DR. SANTANA: I was just going to address the issue of clarification. I didn't understand if what you were addressing was what kind of information you would bring back to us to keep us in the loop or what kind of information you would bring back to us to make a judgment.

To me those are two different things. The latter is more the study section model and in which you have an independent body that helps you resolve the things that the study section can't resolve in terms of prioritization or allocation of cut lines or

things like that.

To me that's very different than coming back to the committee and saying just like you did today, "We don't want you to look at the list and tell me whether it's appropriate or not. We want you to help us figure out whether the process is working okay or whether we need to change the criteria in terms of what's important or not important."

To me those are two separate issues, and I need to get a clear point from you whether we should be addressing both or just one or not.

DR. MURPHY: Well, we will report o you annually as to where we are because we think that's part of this committee's contribution in pediatric drug development, is understanding where we are going, what kind of information we're getting, what kind of products are getting studied. So we will report to you annually.

I think since this process now involves NIH and study sections, is there any other activity that you would think you should play? And the answer may appropriately be, no, let's see how this plays

out.

But the other option would be would the committee consider if we went out, as I said, and we asked all of these people, additional groups, what are your top five drugs, and we ended up with 50 more products.

Maybe one of the things we would do is come to you with a new list, and this time we would say, "We'd like you to think about the criteria that you told us to apply and see if you can help us in resorting or ranking these 50 other products."

That may not happen, but I'm just asking if this committee thinks that is an appropriate utilization of your time and interest, and any thought, you know, about it.

Because you're right. It is a very different activity

DR. NELSON: I think you may have started to answer the question that I had, which is what the kind of nature of an appeal might be. I could imagine a group like this, if not this group, being involved in an appeal about the list partly because this is a

public discussion and lists are public items and having that kind of discourse around the list may be useful.

But I can't imagine an appeal of a negative funding decision of an NIH study section. So --

DR. MURPHY: No, I didn't meant that.

DR. NELSON: So I just wanted to be clear that at that level, since the feasibility and the science and all of those things are part of that decision, then I can't imagine an appeal of a negative funding decision if someone has applied to an RFP.

It sounds like you agree.

DR. MURPHY: Yes. It really is asking your thoughts about your role really in that activity as I described where we have lots of possibilities, and clearly as you've heard we think it's inappropriate at this point to try to deal with this mechanism with 500 drugs.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I'm still a little bit, I guess, confused and uneasy because of that. We have a

very daunting or you have a very daunting task in front of you with a January 4 deadline to come up with a prioritized list, the NIH and the FDA.

Working with this group on an annual basis isn't going to get that job done in the next six months. How do you see the next six months playing out? And what is the process within the agencies going to be, and how do you anticipate using whatever experts or organizational expertise that we all talked about here in this next six-month period?

And will you need to publish your draft list for comment at the end of this period and have analyzed or responded to all of the comments by January 4th for the final list?

I'm just asking. What is the process that's going to take place over the next six months between the NIH, the FDA advisors, and so forth, under the Best Pharmaceuticals Act mandate?

DR. WILLOUGHBY: I think you've outlined a problem that we're struggling with right now, and you, if you think about it, have given us a lot of good advice about how we might address that problem.

Right now there is a cadre of lawyers who are interpreting what the act may or may not be interpreted to say about that issue

DR. KAUFFMAN: Well, that should take six months at least, shouldn't it?

(Laughter.)

DR. KAUFFMAN: That's a mistake right there.

DR. WILLOUGHBY: Well, no, it can't because, you know, there isn't a choice just like there isn't a choice about the fiscal 2002 money. It's going to go forward.

But we are working within our institute on that problem right now and, in fact, have a consultation scheduled with other institutes in NIH, which of course represent different disease processes than the ones we think about in child health, also to ask their input in that process.

But my guess is that it's going to be a generation of a list and then vetting it with multiple organizations, and how we're going to deal with the issue of everybody is going to ask for the drugs of

interest to them, I think, is going to be a problem.

On the other hand, I don't think we want an endless process of generating lists and then doing nothing at all.

I also can't see, although I would have to ask the lawyers, whether there's any appeal to the process at all. I mean, there's always informal appeals, you know. You write the director of the institute; you write the Director of NIH; ACOG writes the Director of NIH, those kinds of things.

But I don't envision a formal appeal process like is specified for someone whose grant is not funded or someone whose contract is not funded. I don't envision a need. Again, I'll put that to the lawyers, but I don't think that's going to be on the table.

DR. KAUFFMAN: Will there be --

DR. WILLOUGHBY: Sure, yeah, but as opposed to a binding appeal process, no.

DR. KAUFFMAN: Will written requests be issued during this six-month period while the list is being generated or are you going to hold off on

written requests until a list, prioritized list, is generated, or can that go on simultaneously, in parallel?

DR. MURPHY: As I indicated, we are working off of the present list to move forward as we've been asked to do, begin to utilize this new mechanism and actually see what some of the issues are going to be, and we'll probably have a very different assessment a year from now as to what we, you know, think is working or not working.

But the answer is we are proceeding with these 19 products to, as I indicated, begin issuing written requests for some of them. Some of them we will not be issuing the requests for because, again, just because you list them doesn't mean that we're going to be able to for all sorts of reasons that have been brought up around the table today. But we are going to try.

So, yes, we are moving forward, but that's why we're calling it the preliminary priority list, because we think we need to do that while this other process will continue to move forward, collect input,

and publish a list.

CHAIRPERSON CHESNEY: Dr. Gorman.

DR. GORMAN: Continuing on Dr. Kauffman's nuts and bolts approach and trying to echo something that Dr. Nelson said earlier, as well, there must be a limit to how many written requests you can issue. If this becomes endless, or it must have some natural limit.

Perhaps it shouldn't have any natural limit, now that I think about it, but the number of written requests will have to be limited by the resources available inside the agency, and then the number of studies that can be done will be limited by the economics of the sponsors, the sponsoring companies and the fund.

So what I'm asking is: is there some conceptualization at the two agencies as to how many of these you are hoping to do?

If we generate a list of 600 drugs or even 50 drugs, how many will be reasonably done at the end of five years, realizing that only has seven variables and three dependent questions in there?

(Laughter.)

DR. WILLOUGHBY: You've hit the nail right on the head. As was pointed out earlier, there's $200 million of authorized money which has not been appropriated. This process also is getting underway at the time of the so-called soft landing for the NIH, when the doubling of the NIH budget is stopping.

So there absolutely will be a rate limiting activity, which is pretty much going to be determined by the money available, the money available to act on the preliminary 2002 priority list is about $7 million. We don't have identified money in any budget for next year to pay for additional funding of meritorious applications that come in in response to RFPs. So that part is not mapped out yet.

DR. MURPHY: I just want to make one comment about the number of written requests. Please do not take the number of written requests that we have issued already as the rate at which we can do this in the future.

(Laughter.)

DR. MURPHY: Because, again, we started

with this massive data, four to 500. We were issuing written requests en blanc. In other words, there was nothing studied in the anti-hypertensive. So we issued eight, ten written requests for anti-hypertensives.

So don't try to take those numbers like I just did and come up with we could generate 60 a year because it's not a comparable. We're not in the same place in time or a comparable process.

I think that what we are finding as we have begun to work on this 19 is that if we got one a month out, we would be doing well. And I don't think that's going to happen, and that's really driving everybody to do all of this background research, you know, getting all of their experts together and trying to work through that study design process.

So, again, I think you're right. Our limitations on how many we can generate in a year is, I think at this point -- this is just a guess. I don't want to see this that I said we can never do more than this, but right now, I would estimate one a month because we're not going to have these numerous

sponsors to which we would be issuing the same written request.

CHAIRPERSON CHESNEY: Dr. Glode.

DR. GLODE: I'm assuming, but I may be wrong, that your written requests differ with regard to what you're asking for, and I'm wondering with each drug if, in fact, categorizing them in terms of information needed, you know, is there or isn't there a pediatric formulation right now or is that an issue for this drug? Is a large safety study an issue? Is efficacy an issue, or is just PK/PD an issue for this drug?

And then you tailor the proposal to just what you sort of need for that drug, which, again, sort of is a priority issue, too, that the easy ones -- I think there are some you could get off this list.

DR. MURPHY: We've been looking.

(Laughter.)

CHAIRPERSON CHESNEY: You can tell who the list makers are around the table, crossing things off.

Dr. Gorman, I think you had a question.

DR. GORMAN: No, it was just I was trying to connect the dots. I understand other government agencies try to do this occasionally as well. If I use a dot that Dr. Spielberg gave us several years ago that it takes between three and $5 million to study a completely unstudied drug in pediatrics and I take the dot that you've got one program a month and $7 million, after two months we'll be done.

So I'm not sure in the sense that after that any written requests that come out have the potential to be unfunded.

DR. MURPHY: Steve, please fix that number for us because the range is quite different.

DR. SPIELBERG: Ranges vary. I will tell you without breaking confidentiality, you can add zero behind some of the programs that we're now involved in and more for a full pediatric development program.

And you know, the old saw that you saw -- bad choice of words -- the information that was being put out on the standard, you know, PK study, you know, $190,000, that was based on doing adult normal volunteers.

You take that into the pediatric population just because you have to do it in, indeed, the right kinds of pediatric centers, et cetera, and because you have to develop new analytical methods for micro volumes, et cetera, et cetera, even the cost of doing that kind of simple PK study goes up way high.

So, again, cost of studies are very, very dependent on the number of patients. I just finished a study of 150 kids at 90 centers. Okay? It was one, point, you know, three kids per center, but that means that I had to send out monitors to every one of those centers whether they were recruiting or not, and every time they recruited we obviously had to make sure of the quality.

So it required sending out QA people, as well as clinical monitors. So costs can, indeed, be extraordinary.

And, again, you know, that's why the issue with these older drugs for which we do have a lot of experience, and I agree that some of that experience may be absolutely wrong. Some of the literature may be absolutely useless, but if we're going to do this

right, we really need to take maximum advantage of everything that's there and, again, fill in the gaps.

And there may be some compounds where the cost of the studies are going to be relatively modest. But, again, remember those studies are going to be done in pediatric patients at good centers, and that does add on significant to the cost and well it should because we want to get this done right. We don't want to use the standard adult PK normal volunteer model. This just doesn't apply here.

But the issue is going to be to take full advantage of everything that exists and then define the critical missing information, not what would be nice, but what really is critical, what would harm a kid coming into an emergency room with dobutamine, or is there even though -- you know, I don't know the field. I don't deal with these drugs -- but is there actually enough information out there right now to write a cookbook for a guy in an emergency room of how to use it based on everything that's now known, as long as you know how to monitor blood pressure and urine output.

So, you know, I think for each of these that's why in a sense Dianne has a daunting task ahead to get each one of these done right, to ask for the information that's needed, to not ask for too much, and also certainly not to ask for too little because at the end of the game, we want to be able to write good labels for these drugs.

DR. MURPHY: I did want to put a different boundary on it though because when I was trying to find our report to Congress, we asked a number of people besides PHARMA, CROs, you know, what the boundaries are on costs, and there are, as everyone keeps saying, there are some studies that are in the less than $1 million for children, and I think you all know there have been some states where we've been able to get good PK information.

DR. SPIELBERG: Sure, and again, if we have a lot of guidelines already, we're not starting from scratch.

DR. MURPHY: Exactly.

DR. SPIELBERG: We have a lot of previous information, and all you want to do is validate

something, you can do it very inexpensively and get those bucks to spread across many, many compounds.

So doing the older compounds, particularly on the basis of good information and particularly since we have safety information accrued over time, both FDA's AE reporting, as well as what's in the literature, that will help us hone down and be much more specific than if we're working with a new chemical entity.

CHAIRPERSON CHESNEY: I think Steve makes a very good point in terms of the dopamine issue and the emergency room. So there may be a lot that we can do with what we have, even though it hasn't been technically tested.

I understand the question you're asking us, which is how do you really prioritize these with respect to importance.

Dr. O'Fallon.

DR. SPIELBERG: How badly is the data needed? And I think that's going to be the issue with each of these.

DR. O'FALLON: And I think we've lost

sight of the fact, I think, that we made suggestions up front that there were certain components or criteria that would be considered important, and it seemed to me someone mentioned briefly that there be perhaps a score, some sort of a scoring system that be developed that would help to rank the need for these agents.

And then within that, then there would be this business about how much bang for the buck can we get here. With a couple of little things in here, we can fill out this one and get that one, get something in this area.

It seems to me it's the area, the disease area that needs the criteria, and then there might be two or three different agents that would be, you know -- are possible candidates for treatment in that area of disease.

It just seems to me that you've got to go back to the importance of the disease defined as not just volume and severity, but some of these other issues as well.

CHAIRPERSON CHESNEY: Dr. Willoughby.

DR. WILLOUGHBY: I wanted to make two more comments on the fiscal issue. One is that we have a number of networks, as do other NIH institutes, that already have infrastructure support and populations recruited. So we may be able to maximize some of the dollars' usage by going to these networks and offering an opportunity for the study to be done there if the sponsor declines.

Also, if the sponsor wanted to do a study and wanted to come to one of our networks and propose it, that's something that could be considered as well.

I can also tell you that as you well know from Civics 101, the federal budget is a year-by-year item. I know what it is for this year for this activity. It's about $7 million. I don't know what it's going to be for 2003 or who's going to weigh in on that issue.

So, you know, we're proceeding because we want to be ready to seize the opportunity if it's there. Are we worried? Absolutely. But, you know, it's something we've done before with other diseases and other mandates and other concerns.

CHAIRPERSON CHESNEY: I think the comment about networks is maybe another criterion, something else we could add to criteria, because somebody mentioned this morning the neonatal network, and if it would be very easy to feed a drug in and get an answer relatively inexpensively into one of the networks as you described, that might be, again, a reason to cross it off the list. It's easier to do.

DR. WILLOUGHBY: Yet another issue is sometimes advocacy organizations can be brought in to offer co-funding if they're interested in a particular drug. It's not a huge volume; it's not a frequent occurrence. But, you know, on a single drug, it might be important.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I just can't remain silent being a member of the PPRU network and let you by with saying it would be really cheap to do this in the network.

The only way it's cheap to do it --

CHAIRPERSON CHESNEY: I didn't mean to imply that.

DR. KAUFFMAN: The only way it's cheap to do it in a network is when the individual sites in the network subsidize the study, which we can't afford to do anymore. So it still costs to do it.

Plus, if we do the whole study without a sponsor, we have to set it up, monitor it, do all of the record keeping, all of the GCP monitoring, write the report, you know, do much more than we do if we're just working with a sponsor.

So I wouldn't walk out there saying we can do it cheaply in the networks. You do have an infrastructure that gives you a place to start. You have a patient base. You have investigators and so forth, but that doesn't mitigate that much of the cost of doing the study de novo.

DR. SPIELBERG: Yes, Ralph brings up a good point. When we're quoting costs of studies, those are external costs. Those are not all of our people inside, the FTEs that do all of the stuff that Ralph's talking about, monitoring the studies, QA, statisticians who write up the statistical stuff, medical writers, all of the stuff that's necessary.

I mean, you're really starting off with no GCP infrastructure to lead to a labeling process. So these are different kinds of studies, and so those personnel are going to have to be generated somehow.

CHAIRPERSON CHESNEY: Forgive me. I misspoke.

Dr. Willoughby.

DR. WILLOUGHBY: No, you didn't. You're right about what you say about the PPRUs, of course. There are other networks that NIH supports, neonatal intensive care network, the maternal-fetal network. NIMH has some research networks. We have an adolescent trials network. We have an HIV clinical trials network. We have a global network.

I think one of the things that's going to be important to do is with each one of those networks, make sure that pediatric drugs are on the radar screen, and to see what advantage we can take of money already set aside in a network that might be interested in doing, you know, one of these studies.

So you're absolutely correct in what you say about the PPRUs, but I think there are other

networks where this might work out more easily, of course, if you can interest the committed groups of investigators who are there after a competitive process to be invested in doing that study with the resources that they already have.

DR. KAUFFMAN: The difference between the PPRU network and the other networks is the other networks are fully funded through the institute for the work that they do for their protocols. The PPRU network has infrastructure support that depends on additional support for doing the individual studies.

So regardless of which network you use, there would have to be funding allocated for the cost of doing that study within that network. That was my only point.

DR. WILLOUGHBY: That's true, but what about if the interested group of investigators says that they'd like to move to the top of the list for how they're going to use their $6 million for the study of a particular drug? We can't force it, but we can ask people to consider it.

CHAIRPERSON CHESNEY: Dr. Luban.

DR. LUBAN: One additional potential source might be the PCRC as well. I don't know whether you -- I mean, they're sort of an NCRR, and nobody thinks about them too much, but that's infrastructure that's already supported, as well.

Oh, Pediatric Clinical Research Centers would try the pediatric parts of the general Clinical Research Centers' GCRCs.

CHAIRPERSON CHESNEY: That's an excellent suggestion.

We have one such center in Memphis, and they're always asking us, you know, "Don't you have any studies that we can do through the center? Don't you have any studies?"

Their funding is dependent on a number of studies. That's an excellent suggestion.

Dr. Murphy?

DR. MURPHY: Thank you.

(Laughter.)

DR. MURPHY: No, really, we've gotten not only some good suggestions, but also some daunting reality testing once again, and we do appreciate all

of the thoughts that the group has provided to us.

I did want to make sure we did get to hear from our colleagues from Europe though, and we are required by law to give you an update, for those of you who can hang in here. So I didn't know if you wanted to take us up on that break. I guess you need to ask the committee.

CHAIRPERSON CHESNEY: Do you want to take a break or do you want to --

DR. MURPHY: I would ask if the committee wants -- we mentioned before, Julia and Agnes. Can you stay 15 more minutes, ten?

What do we need, a five or ten-minute break?

CHAIRPERSON CHESNEY: Let's take a ten-minute break, and don't anybody leave before we meet our European colleagues.

So we'll be back at 20 after five.

(Whereupon, the foregoing matter went off the record at 5:07 p.m. and went back on the record at 5:20 p.m.)

CHAIRPERSON CHESNEY: Dr. Roberts is going

to introduce our European visitors to us.

DR. ROBERTS: We're very happy today to have two people from Europe whom we have worked with, Dr. Julia Dunne, who's up at the podium.

And Julia was a member of the expert working group for ICHE-11, and that's where I first got to know her and to work with her, and currently has just recently taken a job with the European Commission.

Dr. Agnes St. Raymond, who is seated there, is with the European Medicines Evaluation Agency in London, and Agnes actually came and spent a week with the then pediatric team, which was all of five people, and we were still part of the Office of Drug Evaluation IV.

And she is working very hard over in Europe, along with Julia and several others, on the initiatives that they have ongoing, and we asked them to update us and you all as to where they are with respect to their initiatives.

Thank you very much for coming.

DR. DUNNE: Thank you, Rosemary, and thank

you very much to the FDA for inviting Agnes and I to come to speak to you today.

Agnes and I are very excited, Steven, to be in a room that's lit by electricity because coming from Europe --

(Laughter.)

DR. DUNNE: -- it's quite a treat.

DR. SPIELBERG: I'll never live this down.

DR. DUNNE: It's quite a treat.

DR. SPIELBERG: Actually we had to feed the gerbils at the break though to keep them in the wheel.

Dianne asked me to give a very quick overview of the European Union and its legislation.

Next slide, please.

And you've got quite a bit of information in one of your folders of background. So I'll just highlight the points which are of relevance to our pediatric initiative.

So currently there are 15 member states, and they are listed right there. And you may not be aware, but by 2004, there will be another ten. So

there will be 25 members states.

Next slide, please.

And for those of you who prefer your information in sort of pictorial form, this is a geographical map of the EU at the moment with 374 million citizens.

Next slide, please.

And after enlargement, that's what it will look like with 450 million citizens.

Next slide, please.

The European Union is built on an institutional system, and it's the only one in the world that operates like this. And the member states delegate sovereignty for certain matters to these independent institutions, which represent the interests of the union as a whole.

The basic institutional triangle is up here. So you have the European parliament, the council of the European Union, and the European Commission, and very briefly, for the purposes of our later discussion, the European parliament comprises directly elected members from the member states, and

it shares legislative powers with the European Council. So it is responsible for agreeing legislation.

The council of the European Union is the main decision making body, and it embodies the member states. So member states' representatives usually at ministerial level, Secretary of State level, are on various councils which deal with different issues, such as health or industry, enterprise, economics, that sort of thing.

And then the European Commission, whom I'm representing today, is described as the driving force in the system in that it initiates the legislation.

Next slide, please.

And the European Commission comprises a college of 20 members. These members are known as the Commissioners, the European Commissioners. There's a President and Vice President. They're appointed by the member states, and approved by the European parliament, and they have a five-year term.

And then the administration is carried out by a sort of European civil service, which comprises

general services, such as legal services, and the Directorates General, and we fall into the DG, Directorate General, Enterprise. That's where the Pharmaceuticals Unit is. And each Directorate General has a Director General.

Next slide, please.

In terms of the legislative process, there are three steps. The commission makes a proposal. This is adopted by the competent institutions. In our case it will be the European parliament and the European council, and then the member states implement the legislation.

Next slide, please.

And that just gives you the article of the treaty establishing the EC, which sets out the sort of legal text that we have. So we have regulations and the example there given is the regulation which establishes the European Medicines Evaluation Agency, and the centralized procedure we have for authorizing medicines.

Regulations are legally binding, word for word, in the member state. And we have directives.

The directive cited there is one which embodies a lot of our -- a codified directive embodying a lot of our pharmaceutical legislation, and directives are implemented in the member states with national provisions. So there's more flexibility with a directive.

And then there are decisions which are legally binding, and the Commission will issue a decision, for example, to give a central marketing authorization for essentially authorizing medicinal product.

Next slide, please.

The stages in the legislative process are that, first, there is the Commission proposal. I won't go through this slide in detail, but it's the Commission's right of initiative, although sometimes the Commission is prompted to propose something by the European Council, for example, nd before the Commission finalizes its proposal, it will consult.

Now, there are no strict rules or formats as to how it should consult, but it will consult the stakeholders before finalizing its initial proposal.

Next slide, please.

The legislative procedures, there are four different ones, but the ones that interest us are the co-decision procedure where the European parliament and the European Council are co-legislators on an equal footing. So we have to have agreement from both the European parliament and from the European Council -- that's the member states -- in order to be able to get our legislative text adopted.

Next slide, please.

And then an implementation phase depends very much on the type of legal text, whether it's a regulation or directive. A directive, as I've said, has scope for subsidiarity (phonetic). That's where things are delegated won to the member states, a sort of more decentralized way of doing things, and there would be separate national provisions for that.

Whereas with the regulation, you have to refer directly to the provisions in the regulation, and there's no flexibility at all.

There are always time limits and obligations to notify the European Commission about

complying with and adopting and implementing legislative texts, and there are infringement procedures if the Commission discovers that a member state has not implemented a regulation or a directive.

Next slide, please.

Getting onto our current initiatives in the area of pediatric medicines, you'll notice we're slightly more circumspect, and ours is called Better Medicines for Children --

(Laughter.)

DR. DUNNE: -- rather than Best Medicines for Children, but the proposal came as a result of the same recognition that is universal really, that there's a lack of suitable medicines for children, and there had already been various national initiatives in different member states, most notably in France and in the U.K.

And then initiatives at the level of EU. So there was a round table organized by the European Medicines Evaluation Agency in 1997 where a number of recommendations were made, including a need to consider having incentives and some obligations and

other supporting measures in order to improve the situation regarding medicines for children.

There was also support by the EU for the development of the ICH guideline, which has already been mentioned, and in the year 2000, there was a council resolution under the French presidency. Every six months a different member state has the presidency of the council, and this resolution invited the Commission to make proposals regarding incentives and regulatory measures and other supporting measures to provide better medicines for children.

In addition, the European Medicines Evaluation Agency set up the pediatric expert group which Agnes will talk about.

Next slide, please.

The timing of the consultation, why did it happen when it did? Well, we already had some experience from the European regulation on orphan medicinal products, which was adopted in 1999, and we had seen that in the EU incentives can also work for small markets in rare diseases.

And in April 2001, the clinical trials

directive, or the directive which really adopts good clinical practice in clinical trials in the EU was adopted, and that now provides an underlying harmonized framework for clinical trials in the EU, which include trials in children. And there are specific measures within that directive to insure the protection of children in clinical trials.

The Commission is also undergoing a review of its pharmaceutical legislation and the proposals for the amendments to the legislation were finalized at the end of 2001, and it was realized that it would not be possible within the scope of the review to do what was felt to be necessary to improve the situation for pediatric medicines.

And it was felt that what was needed was a separate regulation just for pediatric medicines.

Next slide, please.

So at the end of February 2002, the Commission consultation paper was released, which I think you have a copy of it in your pack. And the consultation paper itself followed a brainstorming meeting with the member states, and that meeting

identified common aims and objectives, and which were put into the consultation paper, as well as possible solutions to the problems which we find ourselves in.

I might say that we had hoped that we would get some benefit from the measures which were being taken in the U.S.; that some of these studies which had been done in children and had enabled you to label products, that some of those might be submitted in the EU.

But unfortunately, that didn't seem to have been the case. So it looked very much as if you get what you pay for, and perhaps we ought to do something about it and not rely -- well, we clearly couldn't rely on benefitting from what had been done in the U.S.

Following the release of the consultation paper, the Commission encouraged input from stakeholders by having workshops and informal meetings, for example, with the pharmaceutical industry, and the consultation period closed at the end of April.

Next slide, please.

These will look familiar to you. These are the possible solutions that have been put forward in the consultation paper: incentives for industry, and this includes an extension of intellectual property provisions for medicines that are still within the patent; and a new idea, which was to help encourage adaptive medicines for children for old medicines which were off patent, which was a new marketing authorization specifically for a child orientated indication or product, and that would be a new marketing authorization. It would be entitled to a new period of exclusivity, but it would only be for that pediatric indication and not for the whole product range.

The consultation paper also raised the issue of legal requirements for companies to perform studies on new products which were in development, and it also discussed public funding possibilities to perform research on old medicines where it was thought that it was very unlikely that even the proposal of exclusivity for pediatric indication would stimulate research by a sponsor.

The next slide, please.

The consultation paper also considered having a central database for clinical trials, well, for existing and future treatments. There is already in the clinical trials directive provisions for a clinical trials database, which we are writing the guidelines for at the moment.

So all clinical trials which are conducted in the pediatric population where at least one site falls within the European Union, those trials will all be entered onto a database, the access to which is restricted to the member states, the Commission, and the European Medicines Evaluation Agency.

This other database, which is referred to in the consultation paper, would be accessible to the public and, again, has not been fully explored yet, but in principle would be a database of existing and possibly future treatments.

The other proposal is to have a new EMEA expert group, which is actually established by the regulation, and that this group would be asked, for example, to identify priorities, advise on trial

performances, suitability, quality aspects and new formulations and maybe organize tenders for research contracts.

And it was also the proposal in the consultation paper that there should be a European Union pediatric network created.

Next slide, please.

Underlying all of this, it will be important for the regulation to insure compliance with the ethical principles which are already set out in our clinical trials directive. We want to insure with the regulation that we avoid as far as possible the conduct of unnecessary trials, and we are aiming for a harmonized approach across the European Union, and to use the existing EU structures, but to adapt them to the needs of this particular case.

Next slide, please.

So where we are at the moment is that we have received all of the comments. We had over 70 sets of comments. They were all constructive. Not all commentators agreed entirely with the content of the proposals, but no new suggestions were put

forward. So it didn't look as if we had left out any brilliant ideas that other people had.

And the current stage is the preparation of our Commission proposal, which will be a draft regulation, which is being done at the moment, and this will be presented to the Health Council. So this is the council of European Union health ministers, which is on the 26th of June. It will be presented orally.

And it is hoped that between July and September the proposal will be adopted, and then we will enter the co-decision procedure, which is extremely complicated and long, and I think it's at that stage when we receive the amendments from the European parliament and the amendments from the European council that we will begin to get to grips with the real problems that our regulation or our proposed regulation will cause.

This for us is very useful, this meeting, because by listening very carefully to what you're saying, we can perhaps anticipate some of the pitfalls and maybe try to avoid them in the writing of our

regulation.

Thank you.

Agnes will now present on the pediatric expert group.

CHAIRPERSON CHESNEY: Thank you very much.

There's a distinct burning smell over here. So plugs were being pulled out and put back in, and that's what happened to your slides momentarily.

DR. ST. RAYMOND: Thank you for inviting us today to share with you the experience we have already in our expert group.

And as I said earlier, it was very interesting to hear you discuss your needs and the priorities because we had this very similar discussion already.

And as Julia has presented, in addition to the complexity of having a consensus of experts, we had the complexity of having harmonization from 15 member states with different histories, different comparators, different level of health care, different system of health care, and different therapeutic strategies and reimbursement schemes.

Next please.

So I will try to go quite fast through the introduction, which is that we have two systems of marketing authorization in the EU. One is centralized, giving an authorization for the 15 member states in one goal, and the other is the national authorization followed by recognition by the other member states, which also allows for marketing authorization similar in the 15 member states.

So two competing systems to simplify everything, and at the end, as you can see, when we have a centralized authorization, we still have 11 official languages. So every decision is translated, what we call the SBC (speaking a foreign language), distinguishes your product information as a different package insert that is for the patients in 11 languages and the labeling on the box.

Next please.

We don't have the FDA. We have a different system. The European agency is serviced by 250 people, but we also work in the network with national agencies and there are thousands of national

experts. So we have a system which at the same time lighter for some things and much heavier to manage than you have here.

Just to go through this quickly, the importance here is that the EME coordinates the scientific expertise and the resources of the member states.

Next, please.

So just a simple design of what you have. You have the expert at national levels. You have the institution that Julia has described. At the center you have the EMEA with the management board and executive director and various sectors, but we also deal with veterinary medicine, but we don't deal with food, nor medical devices.

And we have three scientific committees for the time being, one in charge of the human medicine, the CPMP; one in charge of the veterinary medicines, CVMP; and one more recently created in charge of the orphan drugs.

Next, please.

The CPMP is a scientific committee for

human medicines, is comprised of two members per member states. So that's 30 members, plus a chairman, plus three or for observers from Norway and Iceland who are not part of the European Union, but are still willing to enter one day, so are observers in our system.

Next.

The CPMP is meeting every month, and for four days, and of course, this committee cannot see -- it is dealing with all marketing authorization, preauthorization, authorization, and post authorization, including pharmacovigilance. The committee has a lot of work to do, and works with working groups that meet on a regular basis with a different frequency depend on the group.

And you have the group for biotech products, a group for pre-clinical safety, a group for pharmaceutical quality, what you call CMC, a group for blood and plasma work, blood products, and a group for efficacy, which is dealing with most of the guidelines that we show on therapeutic indication, such as hypertension, for example.

And in addition, you have some expert groups that are adult expert groups that meet depending on the need, and the pediatric expert group is part of this working groups that work on an ad hoc basis.

But you have also I mentioned two or three of them on the HIV products, for example, and a recently created of bioterrorism.

Next please.

So we said we were 375 or four million inhabitants in Europe in the 15 member states, which mean that we have about 75 million children. The situation is exactly the same as it was in the U.S. some years ago. The drugs used in children are not studied nor assessed.

And I've quoted one or two references. The most ancient one dates back to '87, and more recently, the issue of the 1st of June of 2002 in the BMJ you find also some results for the Netherlands and from Germany on the use of medicines in general practice.

And all of them describe the same

situation: use off label or unlicensed, in particular, for products that are used as extemporaneous preparations in hospital pharmacies.

Next please.

So I will go through this one, please.

So this expert group has been created last year. It was decided to create it in May. We received proposals from the various member states, too, for the experts, and the first meeting was in September 2001. It was two other meetings, December and February this year, and the next meeting is at the end of this month.

The objectives of this group are waiting for the regulation to come to start working on the pediatric development of drug, and this includes coordinating at a centralized level, the European level, the national actions and trying to get information from the national actions that have been taken in order to harmonize this action and try to I would say seed, have a sort of seeding system for the other member states.

And we want also to improve what is given