as advice in the guidelines, the existing guidelines, because most of the guidelines that are actually available are aimed at adult diseases and don't include any mention of whether or not there is a pediatric indication and whether or not you can extrapolate data from the adult indication or whether or not you need to perform separate studies and in which age groups.

The second aim is more ambitious. It's to define the need and the priorities for the studies of products, which is exactly what you've done this morning.

The third aim is to obtain some information and to make this information available, in particular, by using your Web site, a common Web site to all member states, and this is just starting with the aim of having this information available to everybody, including the public.

And we have started also to develop a network of relationship with the patient organization with industry. We're meeting with industry next month -- I mean this month -- in two weeks' time to see with

them what is available currently, what practical solution they can offer us and how we can -- for example, we know that some of these companies in Europe have product that they have never brought to marketing authorization authorities, and they have this dossier in their fields, and we would very much like to see them.

We also would like very much to see the U.S. studies that have been performed and never submitted to the European authorities.

And we also when we mean learn societies, we're developing a network with the European Confederation of Pediatric Specialists to be sure that we have the proper expertise all the time in various domains because our group is a very small group.

Next please.

It's actually comprised of 14 experts, which is not much, and we have one representative from various committees or working parties because we want to make sure that what is done in one group is consistent with what is done in our group.

So we systematically invite people from

quality, to be sure that what we will do with them on pediatric formulation will be translated into the proper guideline, including medicines in general for adult or elderly or children.

As I said, the experts were proposed by the member states, and the decision was made for the groups not to have what is the normal way we constitute a group in the EMEA. We take one representative per member state, which means obviously if one member state doesn't offer an expert, we are not obliged to have one per member state, but they have the opportunity to have one per member state.

And this time we create a sort of revolution because we decided that we want some expertise, and we define a priori the need that we wanted.

Next please.

So we decided we need someone that would be able to talk about pediatric formulation, but also have the proper link with the outside world, and actually we have one pharmacist with part of the European Society of Clinical Pharmacy and with the

hospital pharmacy they can relate with this network.

We have one pre-clinical expert plus someone from the safety working party, and you will see in the next slide what we asked them.

We have taken one expert. This is an arbitrary choice of taking Bayesian methodologies, but the idea was to have someone interested in the methodology for small sample size because this is a very important topic. Within that we should go on with new methodologies or methodologies that are not so new, but are not so much used, in particular, with respect to market authorization applications.

And we can go away from the parallel group design.

We have some PK and pharmacology specialists. One is even a professor in Columbus University, John Von Danker (phonetic), and he's also Dutch. That's why he is a European expert.

(Laughter.)

DR. ST. RAYMOND: We have several members of various specialty neonatology because we felt it was important. Immunology; we wanted to have an

oncologist, but we never found one which was available for us. They all have too much work to be there, but we know that we have the proper contact if needed.

We have also two people representing pharmacovigilance, and this is particularly important because we feel that there are a lot of issues that need to be developed in respect of the follow-up of drugs post marketing, especially for children where growth and maturation have their interaction with the long-term effect of the drugs.

And one of these experts is also an expert in vaccines. So it's particularly relevant for pediatrics, and as I said, we have also the links with the existing working parties, and we have decided at the difference of other groups to have an open group because in general we like secrecy. In the EMEA, we don't have the public. We don't have a representative of industry, and our debates are secret. And most documents are classified confidential.

So we've decided that this time the information was very important, and we have always accepted people, experts, I mean, who were interested

in participating in that group and provided that they fill in the proper confidentiality agreement or declaration of interest, we open the group to people who can come and participate.

Next, please.

So for the expert in formulation, we have started working on sort of guideline. It's not much, I know, because guidelines are always guidelines. They are not binding and, therefore, nobody feels obliged to comply with them.

But at the same time, we don't have a regulation yet. So we're more preparing the work and harmonizing our views on what is needed, and we are working on the documents on the pediatric formulation of choice, in particular, with respect to excipients that can be used in neonates, infants and children.

We have used what has been published by the hospital pharmacies in Europe or a network of hospital pharmacies. They have looked at the 20 most requested extemporaneous preparations for children to see where the needs are in the hospital.

This is not representative of the public

label practice prescription, but it's already a need from adult medicine that are every day transformed into some sort of mixed, crushed tablets, and IV formulation and so on.

And we feel that there is a need to work that could be also a starting point for us in the needs for children.

Although this is not the aim of this group obviously to work with extemporaneous preparations, we feel that there is a situation where sometimes it would be impossible to get to a pediatric formulation, and we have to be realistic and give some advice on how to prepare extemporaneous preparations in the best way possible for children.

But this is, as we would say in French (speaking French), by default, I would say.

Next please. I'm nearly finished.

On pre-clinical issues we have worked on the toxicity in juvenile animals. When you put together regulators, they're always happy to add requirements to industry and say do more studies. That's what we want. We feel more comfortable if we

get more information.

But we have also asked the people to review the existing data of studies in juvenile animals to be sure that what we are request has an value, and I think the example of the quinolone should make us very cautious about relying too much on juveniles anymore because the data were in a way informative, but also in a way not informative.

Next, please.

A methodology. This small sample I just alluded to is a common problem also with orphan drugs. As I am already in charge of orphan drugs, we have decided to have a meeting, an inventory of the existing method of what would be applicable to a medicinal product. The meeting will take place in October of this year in the EMEA.

Next, please.

For the needs, I mentioned it earlier in my intervention, and I think we are currently trying to harmonize what has already been done by the U.K., France, Sweden for information on extemporaneous preparations, the existing compendiums that are for

pediatric drugs and some of the U.S. studies, provided they are submitted, and we are trying to define the best way to find needs at the European level, knowing that there might be differences between the U.S. and Europe as regards comparators, the way that people are treated on each side of the Atlantic.

We know it's difficult. Some people have failed to do so, and we are perfectly aware of that and trying to make it simple and to make it arbitrary because we can't be fair. We can't include everybody. We know that will be too much.

And so we've tried to look at the main area. I mentioned pain, for example, to be sure that we have treatment of painful children for all age groups, and that would be the first way into the needs.

This is also in preparation of the public funds that are planned into the regulation, the new regulations, and where the fund will be available, we want to be ready to do the studies by having already defined the needs.

Next, please.

But yet as I said, we have tried to develop and set some guidelines how to follow and where to follow, what should be the endpoints to follow drugs in children.

next, please.

We plan to have that basis also in the regulation, and we want to, as soon as we get the information on pediatric drugs, to put it on the Web as much as possible, and we are very keenly asking the European Commission to have the right to put every information obtained through the incentives and including negative information.

I mentioned the pediatric EPARS. That would be a way out, not including the information in the product information, but to have a sort of scientific summary similar to what we have already for all products that are approved centrally, where you have a scientific summary, scientific basis for the positive -- the granting of authorization.

And we feel that there might be the possibility of having such a resume, such a scientific summary on the Web that would explain what was a

study, what was its result, whether there were negative or positive, and without necessarily introducing that into the product information.

Next please.

So I'm finished. So we've started to work in a practical way in a small group with limited means, but people are very enthusiastic, and I think we can at least prepare for the regulation because, as you know, our legislative process takes several years before it comes to force.

Thank you.

CHAIRPERSON CHESNEY: Those two presentations were superb, and it seems miraculous to me how much you've accomplished given 15 member states and having to get all of those people together, to agree, and the superstructure you've developed is incredible.

DR. MURPHY: Agnes, I learned something. I always learn something from you, but I was particularly taken with I guess Julia made the comment or you that the products that we have had labeled are not getting labeled in Europe. Is that -- I mean

that is something maybe we should pursue as a joint thinking process because I think clearly the ethical issues involved in not conducting additional studies is important.

DR. ST. RAYMOND: I mean, it's quite a problem. We don't always know, and if there's any way we can check on your Web site to find out what's been authorized, and then we ask to find out whether anybody has submitted in the EU because it wouldn't necessarily have to be a centralized authorization.

But we have found out that these studies just aren't being submitted, and I did once -- I didn't do it personally, but I asked a pediatric pharmacist to contact the company because I knew that they had recently got an authorization for pediatric formulation of a particular product which would be very useful, and he contacted the company and they said they have no intention of submitting an application anywhere in the EU. They just got their authorization in the U.S., but they have no intention of submitting it in the EU. And they didn't give them a reason. They didn't have to.

But it's very, very disappointing.

DR. MURPHY: It's quite disheartening.

DR. NELSON: but it's entirely rational. I mean if I was advising a sponsor, I would say wait until the legislation would give you exclusivity in Europe so that you get additional cash. So I'd wait a few years for the process to take place and then submit it.

DR. ST. RAYMOND: Yes, but we're not going to give it retrospectively.

DR. NELSON: So you're going to repeat the same studies that have been done?

DR. ST. RAYMOND: No, no, but it's unlikely that they would get exclusivity retrospectively. These provisions will come into place once it's been adopted, and it may well be that it's off patent. So they won't be able to get a retrospective --

DR. NELSON: Right. I mean, it would still be on patent at that time.

DR. ST. RAYMOND: Well, I don't think it will in this particular case because this is already a

couple of years ago. It will be another couple of years before our regulation comes in.

CHAIRPERSON CHESNEY: Dr. Murphy is going to give us a five-second update.

DR. MURPHY: I will try to go as quickly as possible.

The Best Pharmaceutical Children Act we will not talk about anymore. As I said, tomorrow we will receive training, and Dr. Roberts is going to say something at the very end of the session about what you guys can expect tomorrow.

The next slide, please, Anne.

We also wanted to make clear to everybody that the pediatric rule remains in effect. If you live outside the Beltway, this probably wasn't a big to-do, but inside the Beltway, it was quite a raucous for a number of weeks because FDA has been challenged by the Association of American Physicians and Surgeons in the Competitive Enterprise Institute and Consumer Alert that we lack the authority to enforce the pediatric rule.

I will not go into any further statements

on this, except just to say that at the end the Secretary of Health has announced that FDA will continue to defend the pediatric rule in court and will not pursue a stay of litigation. So the rule does remain in effect.

Next slide, please.

Speaking of the rule, why do we think it's important? We think that it has contributed to the entire effect, as we have often said, of having this incentive and regulatory approach that the sum is greater than its parts or the carrot and the stick or whatever you want to call it. We think it also plays an important role, and we're finally beginning to be able to collect some numbers to look at that.

We looked at, between April 1st, 1999 and March 31st of '02, the number of applications that were submitted and whether they had waivers or deferrals or had completed studies in them for pediatrics.

I do want to digress just a minute and say that the person who ought to be up here presenting this is Terry Crazenzi (phonetic), who is our ADRA

within the office and has done a wonderful job. If you have a question, I'll just pretend like I know the answer, and I'm going to turn around and ask her in the meantime.

But basically we feel that the 94 studies complete is important because what we try to look at is can we dissect out what role exclusivity in the rule might play in this, and the cut to the chase is we can ascribe or make attribution to exclusivity, but we cannot make attribution to the rule as a matter of exclusion. So that's the best we can do for right now.

Next, please.

The reason for the deferrals that were listed is that they don't want to hold up, as you know, and by law we're not allowed to hold up the adult approval, and that we will have future studies in children, and our desire for additional data before proceeding.

Now, it may be that you want more additional post marketing data before you proceed. The reasons for the waivers were safety issues, small

number of patients, concerns about this product was an OTC product. It was not self-diagnosable in children, adult indication that wasn't applicable to pediatrics. Clearly, we've gone over those in the past. That's a large number of the waivers. Certainly the complete waivers is because the disease doesn't occur in children.

The fixed combinations which we have problems with, since we don't know how to use any one individual drug properly, we certainly don't think studying the fixed combinations until we understand the individual products is always a good idea.

And then as has been mentioned, literature information, and one of the things that occurs still in this country is that studies will get done, and they will not be submitted. That still occurs.

Next, please.

Examples of indications or disease is waived. We've, again, provided this for you before but wanted to just reiterate types of disease that you would not expect to get to study.

Next, please.

This is in your handout. I'm not going to go over every one of them, but basically these were the applications that were subject to the rule, and exclusivity was granted.

And if you add these up in your handout -- if you'll keep going; the next one. There are two or three of these. Okay -- that it's about a third. So of those 90-some, because these numbers are changing all the time and everybody wants a precise one, but basically about a third of the completed studies were involved in exclusivity.

Now, Dr. Roberts has sat down and mainly gone through all of the indications and tried to say, "Well, what are the other possible reasons that, you know, might be able to exclude?" Like as a pediatric indication, or they submitted it under the old '94 rule and are just getting around to doing it or whatever.

And I can tell you, unless Rosemary corrects me publicly, that it's a very small number that you can actually eliminate. So that at the most, or I should say at last half of these products were

studied because of the rule, that we couldn't make attribution because there were pediatric indications or there was some other cause or because they were involved in exclusivity.

So that's our broad, ballpark estimate at this time, is about half of these products got studied because of the rule.

Well, can we defend every single one of those? No. Again, that's a diagnosis of exclusion, if you will, for the physicians in the group.

Next, please.

I'm going to now go to the exclusivity contributions to pediatric drug development and the development of additional data.

This slide is a summary since we began of all of the proposals that we have received from industry to study products and of the number of written requests which have been issued, and of the number of exclusivity determinations that have been made that we have granted, 58 of these products exclusivity. We have denied eight of them, though we have actually gotten labels from two of these, which

had useful information in them.

And we have now 36 labels that have been the result, direct result of pediatric exclusivity.

Next, please.

This is supposed to have little parens around it and say percentages. Got left off. The types of studies that we've been asking for, again, this number has really pretty much stayed consistent over the last couple of years. About a third of the studies are efficacy studies, a third are PK and safety, and the rest of them, the breakdown between the PK/PD and safety only studies.

Next, please.

We could spend a whole afternoon or more talking about the benefits that we think we have been able to define as far as labeling with the new studies, but I have provided the summaries in your handout. More correctly, Terry has provided the summaries in your handout of what the new labeling changes are that we think are particularly important because they either indicate an increase in mortality, and we did discuss this previously with this group.

With propofol, they indicate that we had the wrong doses that we were using. They indicate that we had new safety issues that hadn't been described before.

So out of those 36 labels, about a third of them, and that's a fairly remarkable number, have important new dosing or safety information, and one of them we have thus far did not improve efficacy.

So the issue there, again, in response to some earlier discussion was it doesn't mean that the product actually does not work. It just didn't work at the dosage that they were studying it at, which happened to be at the drug levels that worked in adults, and that's in the label now.

But if you kept doing what you were doing, it wouldn't work. So that was what was important about it.

So the summary of all of that is a third of the products that we've managed to get studied thus far have important dosing or safety information or, in one case, efficacy information now included in them.

Next slide, please.

I am not going to go through all of these.

It's ten after six, and I think that my threat that you will have to be here until eight would not be appreciated, but you all can read this. It is in your handouts.

Go quickly through the rest of them. Keep going. I think we're missing one from here.

Very final comment before I ask CBER to give an update on where they are with their therapeutics development program, is the reorganization that has occurred. We mentioned this to you last time, that we were forming a new office, and in that office would be pediatrics, counterterrorism, and pregnancy.

That did occur, and we are now placed as the office ped. with development and program initiatives under the Office of New Drugs.

We're going to reorg. again. As a matter of fact, we're supposed to have finished that reorganization this month, and we now will be reporting out of the Center for Drugs, and it will be the Office of Counterterrorism and Pediatric Drug Development.

I will come back and make a comment about why that makes a lot of sense. You've just got to expand your horizon.

And we now have a new -- because of the expansion of the program, we will have a Division of Pediatric Drug Development, which we did not have before, and we're very excited about that. And we have been given a number of FTEs to be able to grow our program within the office. So that is the big, exciting, new development, that we'll have a Division of Pediatric Drug Development and a Division of Counterterrorism.

And the link here is if you all will look at what was up on our Web page under our bioterrorism Web page, you'll see that some of the more important information that the FDA had to provide during the anthrax event was information on pediatrics. How to use amoxicillin, because people suggested using it twice a day when we knew that to mimic the animal models that were used for the adult dosing, that would not be appropriate. So we were able to provide information on amoxicillin dosing up on our Web site,

and also for the preparations.

We are now developing preparations, again, a little bit to what Agnes addresses, the fact you have to be pragmatic, and when you're talking about shipping air loads of product, they aren't going to ship as much suspension as they are solid dosage form.

And so our pharmacokinetics people and our rapid response group have conducted palatability and stability and in some cases bioavailability testing of various home preparations which we will be posting up on our Web for potassium iodide and the doxycyclines.

So we think that this whole area was one which was of great concern during the anthrax terrorist events. So it does make a little bit more sense than one would anticipate in emergencies.

And I think that's al that we have, isn't it at this point? Yes.

Our Web site has not changed. Our new phone number is 301 -- we also moved just because there wasn't enough going on. We also moved and our new phone number because we don't have cards yet is (301) 827-7777.

PARTICIPANTS: Wait.

DR. MURPHY: (301) 827-7777.

DR. SPIELBERG: That's easy.

DR. MURPHY: And if you're calling Counterterrorism, it's 7711. So --

DR. SPIELBERG: Does that mean CDER doesn't exist anymore? It's not a Center for Drugs?

DR. MURPHY: Pardon? No, no, no, no, no. We're just abbreviating to get things in the boxes, you know.

DR. SPIELBERG: Okay. It still is CDER.

DR. MURPHY: Oh, yes, yes, yes. You know, trying to create the org. charts and little boxes.

CBER, yes. We're through.

Yes, please.

DR. EASTEP: Hi. My name is Roger Eastep, and I am the Director of our regulatory information management staff.

Dr. Karen Weiss, who is our center lead and expert on the pediatric rule and almost everything having to do with pediatric issues, is somewhere in Erie, Pennsylvania with a broken down van. She was on

her way back from a conference in Toronto.

Because of that I'm here and also Helen Wurst, who is the Special Assistant to our Associate Director for Policy, Diane Maloney, is here, and we're going to present the numbers and probably give you some broad statements on what the numbers might mean, but how well we might be able to answer questions that might come up remain to be seen.

Hopefully the numbers will pretty much speak for themselves. As you can see, the total numbers that we have are significantly less than what you saw for CDER, and that's not unexpected since the total number of applications we receive under the Public Health Service Act to license biologicals is significantly less than the number of new drug applications that the Center for Drugs receives.

First I should mention, and I'm sure you're all aware that the pediatric exclusivity relates only to drugs approved under 505(b) of the Food, Drug, and Cosmetic Act.

We do have some new drug applications in the Center for Biologics, but virtually all of those

relate to blood banking and blood products. They're anticoagulants in blood banks; they're rejuvenations, blood additives, and so most of those are really not going to have issues as far as pediatric exclusivity.

We have not sent any written requests out, and we don't see any going out on the horizon. So primarily what we have to deal with is the pediatric rule.

And this chart has three sections in it. The first under received, I just wanted to give people an idea of how many of these things have come into us since the first of April in 1999 that we feel the rule may be applicable to based on the definition in the regs.

And as you can see, we have a total of about 50 applications and supplements, and I've indicated for each of those kinds of applications what sort of decision or determination we've made either finally or initially with regard to whether the data that's been submitted with the application is complete, incomplete, and if it's incomplete or if no data were submitted, what we decided to do with it

with regard to deferring the studies or waiving them.

The bottom line is really what we have to work with. Generally what we do for the applications that come in is we code them in our system as far as whether the information is complete, whether we're going to defer, to waive it. Because we pretty much know from much earlier in the drug development process, even Phase 2 or earlier, what we're going to end up with. So most of these are no surprise.

There are a few though, and as you can see, the numbers aren't totaling up in the pending list or at the total list either at the top. There are a few that we have yet to make a decision on, and that decision, of course, needs to be made at the time that the application and the supplement is approved.

So the ones on the bottom do total up. You can see one situation under supplements there where the total is actually one more than what we indicated it was applicable for, but that's simply because the submitted and complete we had to make determinations on as to whether we were going to defer or waive it.

So we have a total so far of applications and supplements that have been approved of 23, and of those, we've deferred 13, and we've waived seven.

And we don't have any real big surprises as far as what kind of waivers we've granted or the reasons for the waivers. It's primarily based on the limited or not expected usefulness in pediatric, breast cancer, for instance. Our most recent one is botox for wrinkles. We don't expect that's going to be used in kids too much, and so that was waived.

One thing that you might note there is that we have a pretty small number in the approved column or the approved rows for submitted and complete. There's only a total of three, but the pending, and the total obviously, the proportion is higher, which suggests to us that the companies are more on board with the need to submit these up front.

So the most recent ones that are pending tend to be more likely to have completed studies.

I think the only other issue I would mention is, of course, we have vaccines in our center, and as you would expect, a lot of these vaccines are

for pediatric use, and most of those we don't have these sort of issues with. If they submit an application for a vaccine, it's pretty much going to cover the appropriate pediatric population.

That's our numbers with regard to the rule in a nutshell. If there are any questions, we'll try to field them. If we can't answer them, we're going to pass them on to Karen so that she can get back to the subcommittee.

CHAIRPERSON CHESNEY: What are the two agents -- the one agent that was submitted and complete? The second column from the bottom, second one from the left.

MR. EASTEP: Submitted and complete, of the nine BLAs that were --

CHAIRPERSON CHESNEY: That were approved.

MR. EASTEP: I have a list here. I might be able to tell you.

Well, I just have our waived and our deferred list here. I don't have the list as submitted. So that's one we can get back to you on.

CHAIRPERSON CHESNEY: Not a big problem.

Any other questions, comments?

Dr. Murphy, Dr. Roberts?

DR. ROBERTS: With respect to tomorrow, it is a training session for all of you. It will start at nine o'clock in the Advisors and Consultants Building. As Joan announced, you'll be taking taxicabs over there with your luggage, please.

And you will get trained on the Best Pharmaceuticals for Children Act with emphasis on those areas of the act that will directly involve you in your new charges.

And the big part of that session, since the act so nicely lays out a separate dispute resolution process for labeling, if there's a problem with labeling the information and getting agreement of what the FDA feels is necessary to go in the label as a result of those studies, getting agreement with the sponsor.

And so the bulk of the training tomorrow will be really about labeling, and it's going to be presented to you by a group of people within the Center for Drugs who actually does the new reviewer's

course and teaches them about labeling.

And then we will have a representative from a Division of Marketing and Advertising to talk to you about how the language in the label can be very difficult to agree on because that's what actually can be advertised.

You will get lunch, and we will be done by two o'clock.

CHAIRPERSON CHESNEY: Thank you very much.

And I have to just say how very impressive it is, what you all have accomplished in a relatively short period of time. To have 94 drugs approved and with new labeling for pediatric use is just most impressive.

So thank you on behalf of all of us and children.

DR. MURPHY: Thank you all very much for staying with us.

Rosemary says my math is bad, that we're going into our fifth year. It just feels like I've been with you guys for the last five years.

(Laughter.)

(Whereupon, at 6:28 p.m., the Subcommittee meeting was adjourned.)