to 17 inclusive, there will be some information published both at the time the clinical trial is authorized, so at the beginning and also at the time of the results. This is mandatory.

It is not limited to trials performed in Europe, it will also affect any trial performed in the context of the PIP. So, even if the trial is performed purely in the U.S., it will be made public through the European database.

[Slide.]

We have to set up a network of pediatric research which is clearly a different task for us from what we did before and we certainly have started to contact SIOP and ITCC, for example, and all the pediatric oncology groups.

We have to do an inventory of all pediatric users. I am not sure we will gain a lot of information from that but it is more to know where there is a need maybe.

[Slide.]

We got some public funding for studies of off-patent, so again a little bit similar to your system with the NIH. We set up a priority list. We set up the list, not industry. We decided which were the needs.

They were classified according to the severity of

the disease, the age group affected, and also the level of evidence already available for the product, so maybe to go for a win/win situation, giving higher priority for product for which there is evidence of efficacy and no major safety issue.

The first round went last year with 6 projects funded, which received between 20 and 30 million Euros, so this is probably 40 to 45 million dollars for 2007 for a period of three years. There will be a new code published in July and the revised list. For this we have been working with the NIH and the FDA to revise our list to try to have a similar approach to these products.

[Slide.]

So, my message is maybe we have started with a high workload but I think for the timing it works. It is a surprise but it works, and we certainly are very interested in pediatric oncology as a model. I would say it is the most difficult case because, clearly, we are not limited to the adult indication. At the same time we have to consider the mechanism of action.

We sometimes lack the proof of concept in adult and/or in children. We would like to have more models of

pediatric tumors but we cannot necessarily have this information. We need to work and to clarify which age groups need to be included. Surprisingly, or not surprisingly, the level of evidence proposed by companies--they propose some open trials, you know--it is a very weak level of evidence that they would try to make us accept and it's not necessarily what we want. But certainly we are looking forward to the collaboration both with you and with the pediatric oncology groups.

Thank you very much.

Clarification Questions from the Committee

DR. LINK: Thank you. That was spectacular, first of all, by how well you have adopted and succeeded with improving on what we have here, also, that you have really hit the ground running. You have only been working since July. You have more things going on--it is really pretty amazing--and also your wisdom of investing it in Euros rather than in dollars.

I did have a couple of questions just to clarify. I actually read the thing that was included, but two questions, one, the timing.

So, the Pediatric Proposal is actually proposed

very early, when you don't even know that the drug is going to be a success. So the question is, is there a lot of pushback about that, because, you know, you are doing a lot of busy work, because many of these drugs are ultimately going to fail even in the adult indication, so is that a problem.

I like the idea, but I just want to know--

DR. SAINT-RAYMOND: No; if you listen to industry, it is a problem. It is a problem of resources. It is a problem of work to be done and, maybe, of course, inefficiency, or lots of inefficiency. You work for something which is going to fail.

The problem is nobody knows which is going to fail and, if you listen to industry on their product at this stage, they are all going to succeed. So it is very difficult to know which one is the one that you should maybe put lesser thoughts on. It is really not that easy task.

I hope that industry is going to increase its rate of efficiency and I think there are issues there that I know they are working on, because of their own interests. The investment is lost.

DR. LINK: As pediatricians, we certainly support

it because it looks like there is a real commitment to actually doing the trials.

The second question, though, is I am not sure I understand the exclusivity that they get. So let's say that industry does the study and it shows that the pediatric indication is unsuccessful. Here, as I understand it, just doing the study, even if the study fails, gives you the additional 6 months of exclusivity.

What about, is that true there also?

DR. SAINT-RAYMOND: Yes, it is, absolutely. If they do what they were asked to do, and they agreed to do, they will get the 6 months extension of their patent.

DR. LINK: If you have a drug for lung cancer and you try it out in Wilm's tumor and it doesn't work, they still get the additional six months in lung cancer?

DR. SAINT-RAYMOND: Indeed, yes.

DR. SANTANA: Kind of a follow-up to Mike's first issue, because the PIPs are being triggered at a time point that is very different than the triggers in the U.S. for BPCA, I fail to see how there could be collaborative work in trying to get similar studies with limited patient resources being done and agreed upon at the same time, because you

guys are always going to be--if you agree on a PIP, you are always going to have a PIP in place even before there is a written request in the U.S. because the triggers are different.

So, doesn't that kind of argue that cooperation may not be possible or that we are going to have to think this differently? Could you maybe elaborate on that?

DR. SAINT-RAYMOND: I think that is why we established the cluster on pediatrics, and we have early discussion with the FDA. Every month we have a teleconference with the FDA to discuss the PIPs and so they can see where we are, and also maybe you have a lot of knowledge on the product because you also have worked before us on certain pediatric issues. So it is important that we exchange this information and we try to build on that.

What you can see maybe in the future is sort of early collaboration to have one single or one compatible, let's say, not identical but compatible development plan that for companies is certainly the best option.

DR. SANTANA: I think my concern is that a sponsor will work with you on a PIP and then when it comes time to work with the agency here, they are going to say, oh, but we

already have this approved in Europe and this is what we are going to do, you know, don't change it too much or--you know, and so on, and so forth.

I think it presents a lot of issues that will require a lot of negotiation and what we want to do is make it very seamless and straightforward, or maybe we should be thinking of changing here.

DR. SAINT-RAYMOND: The plan is modifiable anyway, so that is part of the thing that a company can come back with a modified plan saying we discussed with the FDA, they would rather do it this way, can we find a solution there.

DR. D. MURPHY: I think it is a very important point, Victor, because at this point one of the things that we are trying to convince our colleagues at FDA is that right now the process is mostly driven by the U.S. because of the incentive activities.

But, in the future, we see that it could be driven by the PIP and that that is one of the critical reasons that we need them to support what is clearly not, within the agency--it is not a PDUFA-driven timeline. S we think it is important for them to understand why it needs to be this type of liaison needs to occur and why they need to be

committed to this kind of interactions.

Certainly, the Oncology Group has already been very active in its own cluster and also with the early stages of this interaction with us. But I think it applies to everything across the board, all the drugs.

DR. CURT: This committee has really picked up a very important point. I chair the Life Sciences Consortium with member companies that are all committed to cancer drug development, and we discussed this meeting beforehand in order to bring an industrywide perspective to the discussion.

A real need identified by the consortium members was harmonization between the FDA and EMEA requirements for pediatric drug development. You know, you have heard that the EMEA requires a full development plan through Phase 3 early in the drug's development, whereas the FDA reviewers gear toward safety and pharmacology, and these divergent endpoints in a clinical development plan can really hamper doing global studies in a disease that is not very common.

So, if this could somehow be mitigated in the future, it would be enormously helpful.

DR. LINK: Dr. Adamson.

DR. ADAMSON: I will first echo Greg's sentiments. The early part of either EMEA's or FDA's development plan is simple, it is going to be the same. We are really talking about we need to get some safety and some tolerabilities, some PK, that is easy. Beyond that, it gets complex for everyone. And to be able to know that level of complexity at end of Phase 1, I think would be extremely challenging.

A question I had, and maybe I am not understanding the data. You have done a remarkable amount of work, and I will correct Mike. You have been working a lot longer than before you started, I mean, I am well aware of, and you were positioned to hit the ground running in a remarkable way.

You said that you had, for pediatric conditions and indications, 10 in first line and 9 in relapser refractory. I am not sure I understand that because, when you say 10 in first line, that means you have 10 studies underway in first line, or can you clarify that?

DR. SAINT-RAYMOND: Maybe we can ask Ralf to clarify this issue, because he has done exactly the ground work. He is on the line and if he is still there, maybe he can answer specifically this question.

DR. HEROLD: Yes, as Agnes mentioned, it drops

very easy to your briefly summarized numbers, yes, but we have been presented--we have taken investigation plans that included to take the development also for investigating the efficacy of that compound into the first line treatment, yes, for just about I think a half or less than a half of the application mentioned by Monsieur.

DR. ADAMSON: So, does that mean you have commitments to do randomized Phase 3 trials in 10 indications?

DR. HEROLD: If the commitment is at the level of having at an early stage, strategy that includes to conduct efficacy studies, the details of which are more or less specified at that stage, so some are actually already coming at that stage.

Two of them, I think, if I remember correctly, and others, have included those studies, as I said, as a draft Phase 2 studies synopsis stage. So this is part of the development. But these studies have not been initiated through the greatest part and if, for instance, the preceding studies would indicate that they should not be studied, then, of course, there is no commitment to do some.

Anyway, as Agnes mentioned, we would expect that

modifications would go over to the Pediatric Committee.

DR. S. MURPHY: Thank you for that presentation. It's very impressive and I especially like in your legislation, the inclusion of the orphan indications and the extension there and incentive.

But I have a question which is kind of--I am just not understanding exactly the harmonization between the U.S. FDA and yours in relation to the committees.

In your committee, like oh, my goodness, what a challenging set of tasks they have for just, you know, meeting a couple days a month, because they really set everything in motion, if I understand it, and approve all these plans and everything, whereas, how does that committee--it doesn't seem to have a counterpart in our legislation whatsoever. So we have advisory committees, and we have the--I am still unclear on what the Pediatric Review Committee here is doing.

They don't seen to be comparable. I am even a little fuzzy on what the Pediatric Subcommittee of ODAC is doing. Maybe we could have a little comment on various committees that don't seem parallel.

DR. D. MURPHY: Lisa, why don't you come up here

and join us because I do think we will try to explain the differences, but they are functionally focusing on making sure there is a coordinated pediatric program within the Pediatric Committee that the Europeans have. It functions quite differently, you are right, because they have all these countries and the way they assign the responsibilities for them. I will ask Agnes to give more details on that.

What our PERC is trying to do is functionally very similar but--because what they are trying to do is make sure that when an application, and not the request for now--but when an application comes in, and the company is studying a product in adults, that they have to bring to this FDA internal committee their assessment, their waiver and their deferral.

So, it is the same sort of activity. There are differences in what else we can do in that committee, because we have this written request process we can also suggest that they integrate or not integrate. But the requirement part, because that is what is so different about the Europeans, it is totally, really driven by the applications that come in.

So, our process that is similar also goes to the

PERC as far as looking at those waivers, deferrals and assessment plans. The timing is different, and we can also bring in the written request process.

DR. WEISS: Something that actually Dianne will mention in her presentation that actually I thought was very helpful was--and Agnes will probably confirm this--is that the EMEA and the FDA are really not the same, they don't function the same way, and I was under that misimpression as well.

The EMEA doesn't have a whole cadre of clinical and toxicological experts like the FDA has. So their scientific committee that meets two to three times a month is somewhat similar to all of us in the review divisions who have clinical backgrounds and have been recruited from academia and whatever to come and work at the FDA.

They don't have that kind of body of people. I mean, some people might not think that is a good thing, but, you know, all the jobs that we do, they don't have those kinds of people, so that function--if I am sort of making it too simple, tell me--but that function is somewhat taken over by the scientific committee that meets two to three times a month.

So, that is where you have to think of the parallel in terms of just sort of how decisions are made, recommendations are made, et cetera. I mean, there are some slight differences but I think that is a fundamental difference between the two sides of the Atlantic.

DR. LINK: So, the FDA is relying more on in-house expertise as opposed to outside.

DR. SAINT-RAYMOND: If I may, there are two different systems here. So, for approval of drug, what you say is absolutely true. The expertise is not at the EMEA. We are called in, anything the work of the national agency where the expertise is, like the FDA. So we have decent, I mean, 27 agencies making up sort of Europe and FDA, if you want. But there is a part in each member state, and we bring our experts to the committee to finalize the things, and they discuss.

But for pediatrics, the situation is different. The application comes to the EMEA, we have a team of pediatricians, Gard [ph] is here, Ralf is on the phone, and we are a team of 15, and we do the first assessment.

We prepare the report, the scientific report ourself, first line. Then, we send it to two members of the

committee who have a look and we establish an electronic work group. So one is inputting the data and then second one is also looking at the thing and commenting on the previous one, and so on.

Then, the issues, the difficulties are discussed in the committee to finalize the scientific opinion of the committee. There is a lot of written work but on the pediatrics we have the first assessment so we are actually doing also in-house a lot of work.

So, the system is a bit different from the marketing authorization.

DR. LINK: I think we will have to defer what we are here for, for a later time.

MS. VINING: Thank you. I just want to say congratulations. I think this is so exciting to have this going on across the ocean and collaboration.

I did have a question about post-marketing studies. Do you have any requirements for post-marketing or Phase 4 studies, and, if so, is there a mechanism for compliance?

DR. SAINT-RAYMOND: The pediatric investigation plan doesn't limit its action or its scope to the pre-

authorization phase so it can extend after authorization, so it can include safety studies.

Of course, for reasons of practicality, also to give a chance to the companies to get the reward, we don't extend the PIP over a long 10 or 20 years, it doesn't make sense because they will never get the reward. So what we do is we ask them to put in what we call the risk management plan. I think you have now a very similar requirement, to have a plan for the safety monitoring over years, which can go on and on for a long time.

We specify which areas we want them to monitor-- for example, growth, brain maturation, and so on. We can ask them to do that as part of the commit of the obligations. So they must show us when they apply that they have set up the system.

We don't ask for the outcome of the system, but we ask them to set up. Also, in Europe, we have a 6-month review of all safety data. So we have systems in place which makes it mandatory anyway for companies to come back with the adverse reactions and to discuss them.

DR. LINK: Dr. Smith.

DR. SMITH: Very nice presentation. I had three

questions. One relates to what Dr. Blaney asked before and that is, what do you do with the third, fourth, fifth, sixth agent in class, the VEGFR2 inhibitor, and who decides, and how many need to be studied in children?

The other was who makes the decision about what agent, whether certain agents should go to Phase 3 in neuroblastoma or rhabdomyosarcoma or Ewing's sarcoma.

The third is can you overcommit. Is there a mechanism for recognizing overcommitment to Phase 3 trials, and there are three Phase 3 trials for a disease that just may not be feasible over a decade or two, to enroll to?

DR. SAINT-RAYMOND: The first question was how do we manage when we have a similar request at the same time. We had this situation because the patent was expiring for a number of me-too's and for hypertension, lowering agents, and so on. It's similar, so we had to discuss that.

Our view is that we can ask very closely related but not identical question to each company. So we are not asking them to do exactly the same thing, or asking them to complement the information that we need in children.

So, it can be seen as unfair, but can be seen as better for the children because, at the end, we will get

answers in different areas and progress in knowledge. That's the first thing.

How we decide the area, well, we try to decide, because the company proposes the first plan. So they also tell us where would be the drug as an interest and they can come back with modification which answers your third question, which is how do you know if you have overcommitted. Then, they can come back say this is not what we need to do or we have safety data showing that we should stop here, and that is perfectly acceptable.

I must say our experience in this area--because it is very, very limited.

DR. REYNOLDS: I notice that you trigger the 6 months of exclusivity, that the particular agent has to be approved by all your member states.

Do you see that as a possibility for limiting the 6 months exclusivity making it through, or is it generally that all member states approve an agent?

DR. SAINT-RAYMOND: Most of the new products are now authorized through the agency, which means automatically getting an authorization in 27. So, for all new products, it is not an issue.

It may be an issue for some of the older products which went through the national procedures that we have and where the authorization was not granted in all member states because companies focused on certain, let's say, more interesting markets.

That is maybe the give and take in this issue that we would like them to have an authorization everywhere, to give more to the children. But it will affect probably a few products and limit the possibility to get the reward for a few products--but not that many, and not for the new products.

DR. PAZDUR: All oncology products, by the way, go through the centralized process.

DR. ADAMSON: I want to come back to one of the questions you raised as far as age limits for studies, and I think what might be helpful if it doesn't already exist is a joint guidance on how to do this.

Now, just as drug development for adults sort of lies at one end of a spectrum when it comes to study design from the rest of the drug development world, I think we find a similar thing in pediatric oncology.

We don't want to delay pediatric drug development

to fill buckets that are going to be extremely difficult to fill where they might not be that difficult to fill in different indications, non-oncologic diseases, and the reality is that if we want to try to fill a zero to 2 bucket in Phase 1, we won't be able to do that.

However, we shouldn't have to reinvent this wheel with every drug and I don't think drug companies should be left to try to figure it out.

So, are there opportunities to develop joint guidances as far as for oncology, which, for better or worse, is different than a lot of other disease areas, to give industry some help here?

DR. SAINT-RAYMOND: Thanks for the question because this is really a very hot topic for us. I think probably better than having a similar plan, we should act earlier, trying to define what are the needs, and I think the needs are the same, so if we issue some guidance.

What we have tried to do is to bring a lot of additional experts to the committee, because the committee has expertise, but not everywhere. So, if some have one or two products similar type, we bring in additional expert to help us define what are the needs.

What we intend to do when we have a little more time, we are still struggling with the numbers, is to ask questions to learned societies, to collaborative groups saying help us answer these questions. And we are sharing with the FDA very often. Say we have an issue and the issue that we have is the same for the FDA. Again, it is not a question of region. It's a question of disease or feasibility.

I think this is really the way forward is to try to get consensus from the people who know best and to tell us this is not feasible, this is not the priority, or do it this way, and we are very open to this possibility.

We have, as you know a number of guidelines. We have worked with the FDA on the oncology guideline, and we have an addendum for pediatric oncology which is being revised. All this is getting into our work.

DR. PAZDUR: Could I just share, so you guys understand what is going on in oncology in general with the EMEA? We have monthly meetings with telecons with the EMEA where we go over all pending actions. These would include BLAs, NDAs, pediatric issues, as well as end of Phase 2 meetings.

We send to them our minute meetings, our reviews, et cetera, already. What we are also planning on doing, we met with Mac's team, is also planning on sending people to some of their meetings that they have, for example, in oncology, just as in pediatrics, they concentrate all their company meetings into about two or three days because they need to bring that expertise together from all of the EU member nations.

Instead of having end of Phase 2 meetings and developmental meetings throughout the month, they concentrate them into two or three days. What we are planning on doing is sending people from our review staff actually to these meetings for a discussion, share with them if we have had a meeting before with the company, exactly what we told them, the minutes of these meetings. So we are trying to get this information as much as possible to a coordinated basis so people are understanding what is said on both sides of the ocean here.

Now, that may not be complete agreement, we can't force anybody to agree with us, there are issues, as Mac explained, that may be different between the EMEA versus the U.S., but at least there is open communication between the

two.

One of the options that we have is obviously to send people to these meetings and, you know, have further discussion there.

DR. LINK: That was a great presentation and it is good to know that we pediatricians have a friend at the EMEA. Thank you.

DR. D. MURPHY: We just wanted to make one technical comment in that the BPCA does allow us to request studies for orphan products.

DR. LINK: We are a little behind schedule, but we are due for a break. We will cut the break to 10 minutes, so be back here at 11:05.

DR. WEISS: Agnes is here all day, so we are going to have more time for discussion. So, if there are any more questions to direct to her later today, there is more opportunity.

[Break.]

DR. LINK: We will continue now with Dr. Murphy to give us an overview of interactions that we have already actually seen some of between FDA and EMEA.

Overview: FDA and EMEA Interactions

DR. D. MURPHY: We hope that there will be more clarity about the differences and similarities by the end of the day. That is the point of it. But I have to tell you all that for at least a couple of years, I was listening to Agnes's presentations and I would see all these charts and groups, and I thought I would understand it. Then something would come up and I would say, oh, but then there is another part of it.

I am trying to say they are different enough that it takes a while to integrate how they are different and, until I really went to one of their meetings, that I really began to see functionally how they are different.

I guess if I had to explain it for you all, the Pediatric Committee there is like a little UN. I was really impressed. You know, you walk in and they have got the microphones and names, there is a big, huge room. It is very impressive and it is sort of run, while with us, with our Pediatric Internal Committee, it is everybody comes in the room. It is sort of like a working thing, you know. It is not that you all aren't working, but it is much more informal. We don't have all the fine technology, and they are doing the same thing, but the processes to get there are

very different.

[Slide.]

My goal this morning is to talk about the differences and you have really heard most of that. We just think repetition is probably good, to keep emphasizing where we are the same and where we are slightly different, talk about the interactions in that 30,000-foot perspective, and then respond to your questions about it, talk about the process and scope of work to date.

We are going to begin to give you an idea of the magnitude of what is involved here and the fact that this is just other duties as assigned to our office--this is not anything that is explicit--and what sort of scientific information.

We are going to get into a little bit of nitty-gritty about actually what is on the Excel spreadsheets because I think sometimes that concreteness helps people understand the level at which we are doing this exchange.

The next person to come up and talk, Jean Temeck, is going to give you some specific oncology examples, because Jean is actually the person who is working within FDA to gather all the information when we get these PIPs

from the EMEA.

[Slide.]

The European context, you know, it is just amazing to me. Somebody said you may have 27 countries. But we have 15 to 17 divisions, so we all have our organizational coordination issues. But they do it in different languages, you know, the other really impressive thing-- 23 languages to be exact.

[Slide.]

This is a real picture right out by the EMEA. I stole one of their slides. Sometimes it appears like you have all this information coming in from all these countries at all these different stages and you are trying to coordinate. But this is really art.

When I first went there, I said oh, my God, which one do you look at, you know. Fortunately, I was walking and not in a car. But there is a lot of coordination that is required.

[Slide.]

One of the points I think we were trying to get at earlier is that EMEA is not an FDA, and that the CHMP--and I have a slide that I hope I got it right, Agnes--the CHMP is

actually the group that then does the assessment of the marketing approval.

The Pediatric Committee is informing that group in a way, but the Pediatric Committee is tasked with doing all of the PIP reviews, et cetera, so if I misstated what the CHMP does, I--

DR. S. MURPHY: Could you say what the CHMP is in words?

DR. D. MURPHY: Committee for Medicinal Products for Human Use.

So, that is their authorizing--is that the right word--their authorizing group for the EMEA when they are doing a centralized review process and not a national review process. Again, that is different than what the Pediatric Committee is doing. They do have representatives from the CHMP on the Pediatric Committee because what you hope you will have the authorizing group agreeing with what the committee has asked for.

It takes a while, and I still don't remember what all the initials stand for.

But the member states basically pooled their sovereignty for this authorization process, and that the

EMEA coordinates the existing scientific resources of the member states for this authorization process.

All the parties are linked by an IT network, which I am always impressed with. You know, within agencies we have a problem keeping our IT system working, so I am very impressed that they are able to do that.

That is important because as you heard, they are actually going to be putting up information, too, that we might not be putting up in this country. But it will be going up in Europe and, therefore, it changes that whole dynamic of what is public and our ability to talk about it at times.

[Slide.]

The European regulatory framework--and I am always hesitant when I say this, that is why I keep looking at Agnes for the wrong words--but basically, their centralized process coordinates the assessment by representatives from the member states.

We have divisions that do this and they have this CHMP that does this. Then, the actual recommendation is, as I said, from the CHMP but then the actual authorization is from the Commission.

They have all those steps versus, you know, it comes into the FDA, goes to a division, we make an assessment and send you a letter of whether your product is approved or not approved. And the company can opt for individual country assessment and approval in certain cases, so there are all sorts of different interactions that have to take place.

[Slide.]

Now, differences between Europe and the U.S. pediatric processes. Now, this is what Agnes was trying--we both used underlines here--because the big issue is that we can ask for an indication that does not exist in adults or is not approved for marketing in adults through our written request process.

Now, again, as I explained earlier, the European process is driven by what comes in and it is required. Our process, we have what comes in and then we have this other additional activity, the written request process.

We try to coordinate them in various ways, and we can talk about it if you want, but when this application comes into Europe for an indication that there is not a similar disease in children but there might be another

indication in children for which that product is of interest is where the issue is right now, I believe, as to how much authority they do have to go out and ask for that.

I think what I understand from Agnes is that right now because they are so involved with just addressing all the applications that have to do with those where they do have an indication, that that is an issue that they are going to address after they get through this first phase of it.

So, for us, we have that in place right now, if you will.

[Slide.]

There are slight differences in definitions. I just provided them on the slide. I am not going to read them to you, but basically, we both feel that if we are going to have children in trials, it ought to be for a product for which there is a need.

[Slide.]

There are other processes that the U.S. still has two separate triggering processes, and I keep saying that. We still have the application that comes in that triggers the requirement and we still have the exclusivity process.

They can be one and the same--I will say that again--they can be one and the same so that if, for a product that came in and the only indication that we want it studied in children was the same indication that is in adults, that written request could be issued only for that indication.

But as Lisa explained to you previously, we often had to make a choice whether we wanted--if there were other indications that occurred in children for which there was not an application coming in, that was different, you know, than the application that had come in. And we thought the condition in children that was more important was not the one that was the same as the adult, we could use written request to do that.

Is everybody with me? Okay.

So, if they are the same, and we don't have anything else in kids, then we will be very much like Europe right now. We would just be using our exclusivity to also help drive it.

One other thing I want to say to you, and Rick and Karen--you know, I know the specifics of how your field works. But remember, when you are doing the regular process

where an application comes in, the FDA can make recommendations to a sponsor about what they think this study should be. But the sponsor gets to do what they darn well want.

They are going to tell you the opposite, you know, boy, we wouldn't dare not do anything. But the truth of it is we make all sorts of recommendations that they choose sometimes not to take because they either disagree with it scientifically, they think that they don't need to do that.

In another field, I can tell you it happened all the time. They thought the size effect was bigger, and they didn't want to do that big a study that we were recommending, and they want to do a smaller study because they are betting that the size effect is going to be such and such.

So, they still, in the regular process, get to do what they want to do and submit what they want to do. That's why you will hear us in pediatrics say when we are dealing with the requirement, yes, it's a requirement to do studies, but they can still do the studies they want.

Rick and Karen and them can advise them what they think they should do, but they still can do what they want.

Under the written request process, which is different--well, there is a similarity to the PIP, and I am going to come back to that--is that under the written request process, they have to do exactly what we ask them to do because, remember, they can fail and still get exclusivity. So it's easy to fail, right? And you could get exclusivity for not doing a very good study.

So, the burden of trying to make sure the study is good is on FDA and the written request process to make sure that we ask for a really good study.

Now, the PIP has the same burden because the PIP, they are going to get that exclusivity even though it is required. And the burden for the committee, the Pediatric Committee, is to make sure that that PIP reflects the best study.

So, what I am trying to say is we have actually a bit more authority to get more and to get what we think is best under the exclusivity provisions.

Again, you have heard, I am not going to spend a whole lot of time talking about the centralized process, I hope you understand the differences between the Pediatric Committee in Europe and the internal Pediatric Review

Committee at FDA at this point.

I would just reiterate that their incentive is also linked to their PIP. But again the PIP is triggered by an application that is coming in. In the U.S., only those studies in response to a written request are eligible for the incentive.

[Slide.]

Now, other differences. The European filing of a product--and Agnes pointed this out to you--for an adult indication can be denied if it does not have the required pediatric plan, waiver or deferral, that is not possible in this country. We don't have that.

We have actually said the opposite in a way. We have said we are not going to block access of products for adults with our pediatric approach. So, we have a requirement and they have to give us, you know, their plans to get the studies done, again under the requirement part. But it doesn't block a filing in the U.S.

The European process is asking for more definitive information early. You saw that in the graphic that Agnes gave you, and the U.S. has a required pediatric focused--the PM stands for post-marketing safety reviews with a public

presentation.

This is a whole discussion unto itself. From oncology, you come from a different world with a lot of drugs with toxicities and a lot of very seriously ill patients. And there are many other products out there that are being studied in kids that are not in serious, life-threatening illnesses. They are important to people, but they are not in life-threatening illnesses. So the safety margin becomes even more important when you are doing that risk-benefit ratio.

So, the legislation has a required focus on pediatric safety after a product undergoes the studies for the exclusivity program, and that was just now recently. It was a good idea and they just extended it to the requirement also, the theory being that once a product is out, the first time a product is out, you know, the first year or two is when you find out more about it.

In pediatrics, as we all know, products are often out on the market for the adults and being used off label in kids. But, hopefully, when everybody knows that it is being studied, they know more about it, it might be used in different ways. So, again, you want to see what the safety

pattern might be at that time. So, that is a requirement in the U.S.

[Slide.]

The U.S. mandated pediatric focused review, as I said, it's public. The European approach has this if the product is approved but not if it's not approved is my understanding.

While for us it doesn't matter, remember you can get negative labeling--I shouldn't say that--you can have a negative study, that that information can be put in the labeling so that product still becomes eligible for its post-marketing safety review.

So, if the product is not marketed for pediatrics in Europe, then, it's not obligatory.

[Slide.]

I won't read you the ICH E-11 principles. They are basically, fundamentally, were developed to say we need to be studying products in children, need to be done responsibly amongst all of us and that the children in the trials need to be in the trials--to summarize it a different way--they need to be in the trials to answer important questions and not just because we have the opportunity to

obtain exclusivity in another market.

That, to me, is the underlying real need why we and Europe have committed publicly to trying to coordinate as much as possible, is that children will not be enrolled in trials because there isn't a consent to do so unless those trials are constructed to answer a question that we think needs to be answered.

[Slide.]

So, what are the principles of our interactions? So we have a regular exchange, you keep hearing about that. This cluster was just recently formed. We basically cannot possibly exchange all the information we all have and that is my next--what I am going to try to do is give you an idea what we do exchange.

One PIP alone, the first PIP we got was 500 pages, right, I think. You know, there is just no way we can be getting into a lot of nitty-gritty detail for all of these products. So we have had to define, if you will, the entry level of information that we are going to have for understanding what each other are doing.

[Slide.]

So, we have monthly t-cons with product-specific

focus. During that time we will discuss that a PIP has come in for a certain product, whether there is a written request, what are the waivers and deferrals, were there any other development or safety activities.

These documents are exchanged through a Eudralink, which is a secure link, because the majority of the information is confidential. That is another extra complexity is all I am trying to point out in all of this.

[Slide.]

From August of '07 through February of '08, there were 119 PIPs. Now, we didn't receive the PIPs, I just explained why, we received the information that this product, 119 of them, had come in to the hard-working group in Europe.

We then, again, there is no one in my office to do this work. We just got somebody--Jean Temeck is going to present to you--who actually came to us, thank God, in time to help us with this because it's her job, it has been her job, and then Ann Myers, our other individual in our office, to get information on all these products, 112 of them now that we have provided information back to the Europeans.

Fifty-seven of these PIPs discussed, of which 17

were in-depth or what we call expanded scientific discussions. So, when we say 57, it may be we just need to know a little more about what kind of a trial you are doing on this one because we know our written request asked this and what are you doing, and it doesn't take a whole lot of information, and we don't ask the division to be there.

Jean just gets the information. If the Europeans ask for it, or we are asking, they will get it from their people and they will bring it. So, it is just the people from the various offices at the EMEA, Agnes's group, and then Jean, Ann, and I, and Dr. Nelson also often sits in on these. We don't involve the divisions until we get into what we call our in-depth discussion where it is clear--I shouldn't say it's clear, it's almost never clear--we think that there is a difference in what they are asking or we are asking. We just want to understand something.

We will ask the division to come to these meetings and the EMEA will get their technical experts also to come to the meeting. But you have to have time. So that means it is more than one meeting is what I am trying to tell you that would be involved in that.

[Slide.]

So, monthly, the EMEA sends the FDA an Excel spreadsheet--and I am not going to read this to you--but it gives you an idea of the level of information that we get. We do get down to the indications and the ages and, you know, waivers and deferrals, and we don't routinely get the summary reports, which is something that the Pediatric Committee at the EMEA issues at the end of the 60, 30--at zero, okay, so it's early in the process.

We get those when we are having further discussion.

[Slide.]

Monthly, we send them an Excel sheet which has all this information on it. So somebody has to go--Jean Temeck mostly ends up collecting much of this, in working with the various divisions.

[Slide.]

Just keep going. This is the kind of information that we exchange, you know, the status, whether the holds, if there are safety concerns, who is doing what kind of long-term monitoring, differences at endpoint, differences in trial design, differences in dosing regimen, differences basically is what we end up discussing.

[Slide.]

We do make sure that we are all on the same wavelength and, if we are not, why not, on waivers and deferrals and collaboration on the conduct of pediatric studies, because we do have situations where we know that it is the same trials meaning many centers that are involved in a trial that is going on in Europe and the U.S.

[Slide.]

I am not going to go through all this except to say that we have had--these are the types of expanded discussions where Europe, the ability to ask for a placebo is different. So this is often a big area of discussion of what is your control arm because the U.S. has a different approach for that.

[Slide.]

I have listed anti-hypertensives where we do ask for placebos and treatment of multiple sclerosis where we do ask for placebo arms.

The choice of comparator of active controlled trials and the standard of care. This gets back into some of the difficulties with doing similar trials, what is the standard of care. It is different sometimes.

[Slide.]

Age groups to study, and this has been very interesting because, you know, it may be where people are on their comfort level with going into the different age groups. I can tell you that we had one discussion where I think our European friends convinced our FDA colleagues that they could go lower. So it goes both ways.

An example was the anti-convulsant requested studies in the U.S. down to 1 month of age while the EMEA was proposing including neonates. It had to do with differences in opinion about the accuracy of the diagnosis, so again, you know, in that age group. It often is differences in scientific opinion.

[Slide.]

Indications. This is again another example of indications. In this situation, we actually had information which we provided the EMEA about a study that had occurred with one indication that we think helped inform them about the indication that they were looking at.

[Slide.]

Then, of course, efficacy endpoints, and we have had differences, scientific differences in the type of

endpoints that are requested. Our Cardiorenal Group will not accept sort of a mean. So it's different, and we will hear more about the--you all know the tumor issues more than anybody, so I don't need to tell you about that.

[Slide.]

Then, reasons for failed trials. This is something where we are trying to both bring information to the table about how to better design these trials because we in the U.S. have a number of failed trials, and we are trying to share the information with our European colleagues about why we think they may have failed.

They know about them, and they also have reasons about why they think they have failed.

[Slide.]

This is just again the principles of these interactions are to maximize the information we get out of the best trials that we think we can put together, and to do it in a way that we all inform each other. But you can see from the numbers that this is an enormous workload effort at the moment.

It is one of those things, you know, watch out what you ask for because then when you get it, we have been

wanting this for years.

[Slide.]

This is just to remind everybody this is still an area. The neonate is still, and all of this area, not getting studied because of member exclusivity. You get sort of one shot at it, and this population often doesn't get studied.

[Slide.]

As I said, be careful what you ask for. This child was about 5 or 6 years old in 1977, when the American Academy of Pediatrics said we have to start doing studies in children.

[Slide.]

This is her child, now 1 year old, and this is where we are today. It has been a long haul but we think it has been a tremendous improvement and we are happy about where we are going. We want to also again recognize the work of many people, particularly the American Academy of Pediatrics. There are also many of the pediatric professional groups, subspecialty groups that have worked diligently in trying to make sure that these products get studied.

So, that's it for me.

Jean, do you want to come up here and provide more detail?

Clarification Questions from the Committee

DR. LINK: We are just going to have a couple questions now and then probably we will have more after we have some case examples.

Dr. Finklestein.

DR. FINKLESTEIN: That was an excellent presentation. I have a couple of questions. One is, we heard about the volume exchange from Europe to the United States. Do they get an equal amount of volume going the other way because I heard about the overload factor?

The second thing is, are most of these volumes of exchange for information only, because a lot of your talk had to do with the differences?

One of the things that Mike Link talked about was collaboration and can't we cut out some of these differences. I offer pediatric oncology onto the table because in pediatric oncology we do collaborate with our colleagues in Europe. We do have cooperative studies across the Atlantic and wouldn't that be the ideal field since

networking in pediatric oncology is something that is inbred in us.

Wouldn't that be the ideal field to see if we can start working a collaborative effort so that we aren't doing things differently because, in pediatric oncology, our thought processes are pretty well synchronous.

DR. D. MURPHY: The first thing is, as I said, they send us 119, and we send them 112 back. So, yeah, the exchange is in both directions, the information on that.

As for everybody wants to get to where you are describing, I think we are committed to it because we don't want any child to not be in a trial that's answering a good question. But you guys are so far ahead of the process because of the way you have your networks and the way you do pediatric trials.

The long collaboration that the ability to exchange that information is really going to be something that the Division of Oncologic Products, which are Karen and Rick, and the resources that Agnes has in her pediatric committee, whom she can pick scientifically, you know, what resources she can put to that task, that is really the limiting--I mean, Agnes and Karen, that is the limiting step

right now if I had to what I think is respond to what you are suggesting.

DR. REAMAN: I just have a question for clarification. You, in describing the differences between the FDA and the EMEA, you mentioned that you wouldn't block the filing or the approval if there were no pediatric development plan.

Is it the filing or the approval is my first question.

The second question, who is "we," we, the FDA, we, the United States Government?

The third question is why not, and how do we enforce PREA?

DR. D. MURPHY: Okay. Let me just say probably the key word here is lawyers, but let me go to the first part of it. It is the filing. If somebody comes in with an IND at the FDA right now, they don't have to have any of this really in place.

What has to happen is that--and it's later in the process at FDA, you know, during the review, during the Phase 2/3, so that is by the time they get to getting their approval letter, okay--so it's much later. We try to make

sure it is earlier.

That is the good part about PREA actually, is that PREA says earlier, you are going to talk with the company you are going to try to get all this in place. But where it really hits the fan is what I am telling you is when they are going to have an action, before they can take that action, they are supposed to come to this newly authorized committee and tell that committee what their plan is because, before, the division could say, oh, okay, we think it's a good idea, we are going to study pediatrics for this indication in this way, and, you know, all they had to have really was a date.

So, now they have to come in before that action is taken and have their plan looked at, or their reasons for deferrals and waivers.

What if they don't is what you said, what happens. We haven't had that happen. Most people I think do try to have something in place but, to be quite blunt, I don't think we have any authority to do anything about it. We can just simply tell them that they are supposed to do it.

DR. WEISS: The vast majority I think of applications are basically deferred and sometimes you kind

of know what you might want to study. But you sort of defer and you have dates that are well into the future. But sometimes you don't even know at the time that a marketing application is in for adults, particularly if it is really a new molecular entity.

I think the feeling, you know, you are sort of between a rock and a hard place. You want to get information on pediatric patients if the drug is going to be useful, at the same time, you don't want to expose children too early, particularly if the drug turns out to really have some untoward toxicities that you don't necessarily appreciate. So sometimes you really want to gather more data in your adult sort of human guinea pigs before you expose children to it.

When something is very, very new in its class, you know, you are sort of in unchartered territories, and you are not really exactly sure how much you are going to want to need and when you are going to be comfortable. So the decision of even if to do something to study somebody, a pediatric population is deferred.

DR. LINK: The deferral makes sense, but I think that the Europeans, you know, they have a better stick

because there really is a commitment. They say that you have got to show us what you are going to do.

It can be modified, it can be dropped if the drug doesn't turn out to be anything. But if you are really interested--this is the editorial message here--if you are really interested in having kids get these drugs and having them studied adequately, not just oncologic drugs, you have to know right upfront that there is actually a bulletproof or not quite bulletproof but a 500-page PIP, I guess, in place, that they are going to do something.

DR. S. MURPHY: I have just a question, not an editorial about this information exchange. Okay, sorry.

DR. SAINT-RAYMOND: Just believe that what we do in Europe, we feel is useful for you because the plan will be there. And the outcome is also useful for the U.S. It is not just for Europe.

DR. LINK: We didn't think that your idea wasn't good for us, too, they just do it better.

DR. S. MURPHY: My question is to this information exchange, which is right now so intensive, 119 one way, 112.

Am I correct in assuming this is reflecting just the start-up of the European activity, and that this

shouldn't be sustained at such a high level, it will smooth out, right, or what? No? Yes? Who knows?

DR. D. MURPHY: Well, yes, there is a bolus. I think we can say there is a bolus coming in. But what we found in this country is that in the beginning of the initiative, there was a huge bolus.

But it's a steady process, I mean because you have got new products coming on, which is good, you know, you are still behind in trying to get products studied. And one of the things you are trying to do, if you want to use your exclusivity, is you have got to get them before they go off patent. So you are working to try to get those into the pipeline, too.

Yes, there is a bolus, and there always tends to be. With us, we have a legislation thing, and there is always a flurry right before the end of the legislation. And then there is a nadir for a little while. And then it goes back up again.

But I would imagine in Europe that they are now 10 years behind us, right, as far as our legislation started in '97, theirs in 2007, so they are going to be busy for a while.

DR. LINK: I think we really need to move on. What we can do is we can have Dr. Temeck's presentation of cases and maybe this will give us some insight into exactly what is going on. Then we can have a few questions after that so we are on time for lunch.

Case Examples

DR. TEMECK: Good morning.

[Slide.]

I will be discussing today the interactions between FDA and EMEA pertaining to the development of oncology products in pediatric patients.

Just to put upfront, since most of the information that is exchanged between our agencies is confidential, my remarks will be fairly general. I will not be able really to go into specifics, but just to give you a flavor of the nature of our discussions.

[Slide.]

I am going to be focusing on four areas. One is the common goals that we share. I apologize, you know, for the second bullet. I mean, the point was made that--and it clearly is all in the spirit of collaboration, and we do have many similarities.

Unfortunately, with this presentation, I have focused on some examples where there are some differences in our approaches to the study of oncology products. I will give you some general ideas as to type of information that we exchange and the impact of the information that is exchanged.

[Slide.]

Clearly, our agencies share common goals. We recognize that there is an urgent need for the therapeutic options for pediatric patients with cancer. We recognize that there is need to conduct these studies early in product development. We also recognize the need for process transparency and the need to share in a timely fashion the information that is obtained from these studies.

On the next several slides I am going to provide some examples where we have some differences in our regulatory approach.

[Slide.]

To initiate pediatric oncology studies, EMEA generally requires some proof of concept either from preclinical studies or from adult studies.

FDA, of course, also recognizes that it is

important to have some proof of efficacy that the drug will work in pediatric patients. But we recognize that preclinical studies are not always predictive of clinical response and sometimes, although we may not have an adult experience with the same type of tumor in pediatric patients, we might have some experience in adults and related tumors.

But both of our agencies recognize that there is need to conduct these studies particularly when there are a lack of therapeutic options.

[Slide.]

Now, this is just to give you an example where proof of concept or lack thereof came into play. FDA had issued a written request to study an oncology product for the treatment of brain stem gliomas and EMEA asked us to provide some clarification as to why we had issued this particular written request.

We did acknowledge that there really was not much in terms of proof of concept to move forward with asking the sponsor to conduct this study in pediatric patients with brain stem gliomas, but we emphasize that there are a lack of therapeutic options for patients with this particular

tumor.

And we specifically mentioned that radiation is mainly palliative in this case and does not really confer survival benefit. So we really wanted to move ahead with asking for the sponsor to conduct the study with the particular oncology product in conjunction with radiation in this particular clinical setting.

[Slide.]

Now, again, we have gone into indications and what EMEA can do versus FDA and, at this point in time, unlike EMEA, FDA already has a process in place which provides us with great flexibility in terms of studying a wide variety of tumors, a wide variety of indications for a given oncology product. This is thanks to our pediatric legislative incentive under the Best Pharmaceuticals for Children's Act.

[Slide.]

An example here is EMEA is studying a particular oncology product only for nasopharyngeal carcinoma in children. FDA is studying not only nasopharyngeal carcinoma but also we are studying this product looking at its safety and efficacy in pediatric patients with relapsing or

refractory solid tumors.

[Slide.]

Now, differences may exist in our choice of chemotherapeutic dosing regimen. We have had some discussions with EMEA as to the choice of chemotherapeutic dosing regimens for nasopharyngeal carcinoma and, basically, the dose that we have asked for is similar to that which is already approved in adults for this product, actually, for squamous cell carcinoma of the head and neck.

EMEA has listened to their rationale for recommending the particular dose that we did in this written request. They are taking that under consideration. They have not made yet a final decision as to what they will do. That will be decided next month.

[Slide.]

Differences may exist in the choice of primary efficacy endpoint and again looking at the study for nasopharyngeal carcinoma, we have discussed with EMEA should we use one primary endpoint. And we have asked for a complete response in our written request, or EMEA saying should we also consider survival in this rare tumor. Again, this is under discussion by EMEA and they will reach a

decision next month with regard to this.

The concern that they have raised with us is that here, if you are adding an oncology product to the chemotherapy regimen, might you not incur additional toxicity but not have an additional benefit, and that is why they have raised this issue of including survival also as a primary endpoint.

In the next few slides I am going to focus on some of the scientific information that we have exchanged with each other.

[Slide.]

These are circumstances under which we discuss with EMEA, cases where we would grant a full waiver or partial waiver or deferral of pediatric studies, and this is just to outline for you the conditions under which we would grant a full waiver.

One is, if necessary, studies are impossible or highly impractical to conduct--that is, the cancer is not applicable to pediatrics--for example, breast cancer, multiple myeloma, or there is a low incidence of the cancer in pediatric patients--for example, colon cancer.

The second criteria for issuing a full waiver is

if there is strong evidence that the product would be ineffective or unsafe; or, third, the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.

[Slide.]

Here, I have given you the criteria for a partial waiver and that is when a subset of pediatric patients cannot be studied for any of the criteria specified for a full waiver. For example, there is a cancer that occurs predominantly in a particular pediatric age group so that, in that case, we would just study that cancer in that age group and we would give a waiver to children in the age group in which it was very infrequent or does not occur, or there are reasonable attempts to produce a pediatric formulation necessary for that age group that have failed.

[Slide.]

Now, we have shared preliminary efficacy information with each other. There is a particular oncology product which is under investigation for treatment of neuroblastoma, a Phase 2 study is ongoing and, at this point in time we do not have evidence of efficacy. So we have

shared that information with each other.

[Slide.]

We have also shared safety information from completed and ongoing studies. For example, there is an oncology product for which a Phase 1 dose escalation and safety study was conducted under PREA in pediatric patients with relapsed or refractory solid tumors and we shared with EMEA our safety concerns based on our preliminary review of the data--namely, that there were elevations in blood pressure and proteinuria observed in some of the pediatric patients enrolled in these trials.

And these adverse events are already in the product label because the product is approved in adults with certain tumors. Also what was seen was elevations in gonadotrophins in some of the post-menarchal girls who were enrolled in this particular study and that we both agreed we would be monitoring these parameters in future clinical trials that will be conducted with this product.

[Slide.]

We also discussed safety concerns related to another oncology product for which there are Phase 1 and Phase 2 studies that are ongoing in pediatric patients with

solid and hematologic tumors, including neuroblastoma and also studies are ongoing in adults with a variety of cancers.

EMEA was informed by FDA of cardiac adverse events reported with this product, namely, that we were seeing arrhythmias, particularly supraventricular tachycardia. Also there were clinical and EKG findings of cardiac ischemia.

[Slide.]

The goal, of course, of sharing the scientific information is that we may alter as a result of the sharing of information, the conduct of an ongoing trial, or it may help to guide the conduct of future clinical studies.

Examples are: oncology product for the treatment of nasopharyngeal carcinoma. We have had a number of discussions with the EMEA with regard to this particular product. EMEA has informed us that at this point in time, based on our discussions and their further review, they have rendered a positive opinion with regard to this pediatric investigation plan, however, a final decision with regard to this PIP will be rendered by EMEA next month.

Also, we had discussed with them another oncology

product for the treatment of solid and hematologic tumors, including neuroblastoma. This is the one where we had discussed the cardiac adverse events that were emerging from the Phase 2 trial that was being conducted and that we both agreed that there is need for careful cardiac monitoring in the clinical studies with this product.

[Slide.]

In summary, we share common goals, we collaborate with each other. At times there may be differences in our regulatory approach. We may agree to disagree, or we may actually modify our approach. The point is that we were alerting each other to important critical information that is emerging as these studies are ongoing, as they are being conducted and, hopefully, this information will help to guide the conduct of future clinical studies.

Thank you.

DR. LINK: Thank you very much. I think that shed light on some of the back and forth that is going on that is actually very useful.

DR. TEMECK: Thank you.

Clarification Questions from Committee

DR. LINK: Victor, do you still have a question?

DR. SANTANA: Yes and, actually, I am glad I waited until Jean presented.

Can you give us any examples in the oncology world or the other disease groups where there has been a PIP so far that accurately mimics or similar to what you guys may have requested in a written request?

DR. TEMECK: Oh, yes, there are a number. In fact, I would have to tell you, Victor, I think the majority of the times we really are in agreement.

DR. D. MURPHY: I am sitting here going, it looks like we are talking all about differences. But, you know, when we all agree, you know--we don't want to hear about where we have any differences.

DR. SANTANA: But the point of agreement is the issue of collaborations because there are limited patient populations, there is a limited number of questions.

DR. TEMECK: That is right.

DR. SANTANA: So there are no duplicative efforts. That was the point of the question.

DR. TEMECK: Oh, yes, that is exactly right, Victor, that is the whole point of exchanging this. We do not want to duplicate efforts.

Also, if we have already conducted a study that has been a negative study, then, we want to make sure that EMEA is aware of that because they may want to ask then a different question and design a study, a different type of study to answer a different question.

DR. D. MURPHY: Theoretically, that would be an ideal situation, and one of the reasons that it has really driven this is that we know we only have one shot under exclusivity. As we have indicated, many of the trials raise as many questions as they answer, and certainly the failed trials have many questions.

So, we are hoping that this collaborative effort would result in our European colleagues being aware of what our concerns and questions are and then being able to get trials that would address some of those, not just the different age groups, you know, that is another opportunity is the different age group but also the different scientific questions.

DR. LINK: Dr. Murphy.

DR. S. MURPHY: I would like to ask you about waivers and expand a little because, clearly, there is some kind of judgment involved in giving a waiver, and whether

you have an example of--for instance, you listed on your slide that the product does not represent a meaningful benefit over existing therapies, if you would expand on how you define that, or is not likely to be used in a, quote, "substantial number of patients."

I am just curious, do you have an example of a product like that?

DR. D. MURPHY: Yes; and I think there was a list that was provided by--I think you had it, didn't you, and used in your--it usually comes down to diseases that don't occur in children, or even when we have very small populations, if it is serious disease or there is a real need, we will then say even though it's a small population, it meets the meaningful therapeutic benefit. So, for a waiver, you have to meet both.

To answer you, it is a set of diseases usually that don't occur in kids. That's the usual approach. And, even when we have situations where people think a product may not be--and this is in an oncology one--probably isn't going to be used in pediatrics, if we don't know yet. Sildenafil is a perfect example because it ended up being a product that we looked at for pulmonary hypertension in

neonates.

If we don't know, we won't waive it, we will defer it. You could say how can you do that when you don't even know what you are deferring it for. But if the physiology is such that there is a potential that there is a population out there that we might want to use it in, we would have deferred it in a not exact--it would be a very limited description as to how we were deferring it.

DR. S. MURPHY: That is helpful, but if I could just pursue this because more and more companies are obviously developing drugs not for diseases, but for targets of pathways or something. I mean, I just came from the AACR meeting and everyone now thinks of pathways, not diseases. So we think in pediatrics that we have very important models that have fundamental pathways that will be important for adults frankly.

But if you give them a flat-out waiver, for instance, for some disease or some drug or--well, a waiver for a drug like that they want to license for myeloma in, but it has a pathway that is really fundamental, how could we ever get that studied in children then if the target is later or then identified to be present in both conditions?

DR. D. MURPHY: I think that is a really good point, and I am going to ask Karen to maybe provide, or Rick, some specific oncology examples because it is a struggle where you don't really know exactly how you are going to apply that new knowledge but you don't want to cut off that type of research.

Because we are now required to come up with more specifics to the plan, you would defer with a plan, as I was saying. The bottom line is that if there is a potential, if it is so unknown, and it is new, it would be highly unlikely that we would waive it until we are sure because waivers are hard to reverse is what our lawyers are telling us.

DR. WEISS: Sometimes we have been able to do things under PREA and, again, you know, because we have these two different pathways. But, where we can ask, particularly biologics that aren't eligible for the exclusivity provisions, then, we might see more studies.

But, for instance, for drugs that like affects the VEGF pathways, which probably can be fairly broadly applied, so even though something like Avastin is approved for colorectal cancer, you know, you might be able to ask for something that may be, you know, where there is a role for

something to inhibit that particular pathway, or EGFR expressing tumors, you know, with the idea that we might not know specifically. But there might be down the road ways to identify or there might be some specific tumors that are EGFR expressing in pediatric populations.

So, it's not, you know, like the science is not yet caught up to those kinds of areas but we have some limited ability to do that. But I think you are absolutely right, you know, as the molecular targets become better known.

Rick was reminding me that the specific legislation I believe says it's a disease, it doesn't talk about it as the pathway. So, that might be some option to think about for down the road.

DR. PAZDUR: Here again, are we going to be redefining disease at a molecular pathway, not just call it colon and breast cancer. I think when we evoked an application that is coming in with a specific targeted population that this is indicated only for EGFR-positive patients, then, that would be easy to then translate that into a kind of redefinition of disease.

However, if somebody comes in with a garden

variety colon application with a relative nonspecific drug, it is going to be very difficult to evoke PREA in those situations.

DR. LINK: But the other problem is that there are off-target activities of the drug. You don't even know--I mean, you may think you know what you are talking about. You actually don't.

DR. PAZDUR: That's right. And here again, I think you are entirely right, you know, how many of these so-called targeted therapies are truly targeted therapies or kind of elusive targets that we really don't understand quite well at the time that they are being developed.

DR. ADAMSON: I just want to narrow down a little bit on the differences between the two programs. Yes, I agree there is more flexibility on the U.S. side but that is a limited degree of flexibility.

Until, as Rick and I have heard this from you for many years now, until we get to the point where we redefine disease, or until the legislation changes it, there is a gap because PREA is right now disease-specific and BPCA is voluntary.

So, the flexibility isn't entirely on the BPCA

side and a company can simply say, no thanks. So, we are in complete alignment with the EMEA when it comes to PREA. They have linked their incentive, they have linked the carrot with the stick in the soup and we have separated it. But we both have the same gap and that is going to remain a gap at least until 2012 or until we redefine diseases.

DR. REAMAN: I just needed some clarification about waivers, waivers and the fact that waivers, once they are granted, are difficult to reverse. But it doesn't preclude the possibility of doing a study. It only eliminates the carrot or the stick. But I mean, because a waiver is given, it doesn't mean that a study still couldn't be performed, correct?

DR. D. MURPHY: Right. The waivers are under the required part, okay, and again, as has been pointed out, it is disease-specific right now. So you often are waiving for that disease, that specific disease. But, again, unless you have a known indication in kids that you can go for, you are going to have difficulty getting it under PREA, I guess that is what I am trying to say.

So, you are having to use your exclusivity, because that is what the sildenafil example was. But what I

was trying to say is if there is a hint when you came in particularly in oncology, when you are using it in this more general way--and this is not my field--you know, when you are using it in that more general, that therapeutic agent is going to be used for those types of receptors, even though you may not know what it is in the kids that you are going for at that point, we would tend is what I am trying to say to not waive that.

Also, to let you know that we have had a situation where we have reversed a waiver. Again, this was all under PREA, where we made a mistake, you know, we didn't know and we decided we needed to go back and ask for it.

It has happened. It is much more difficult and we tend to err on the side. But again it's the non-adult indications, the pediatric-specific indications that we are getting under the other mechanism.

DR. LINK: It worries me that you could miss something especially a drug that comes in for prostate cancer, you know, there is no a priori reason necessarily why it is going to be specifically useful for prostate cancer. It may be terrific for Wilm's tumor but, if you never treat anybody, you are never going to know.

Now, we have some preclinical testing that may or may not give us the right leads or we think that is giving us the right leads but sometimes, you know, you don't know until you try, at least that has been the experience that we have had in pediatrics.

DR. D. MURPHY: Again, but that application came in for a very specific indication and so we are only waiving that indication, we are not waiving--you are not waiving Wilm's; do you see what I am saying?

But because the application didn't come in for Wilm's tumor, it came in for prostate cancer, okay? Now, we can't require them under the rule to go out and study Wilm's tumor. We have to go out and get the Wilm's tumor--right, we can wait--but what I was trying to say if there is some other, like in colon, or where you think there might be a pediatric similar disease, we would tend not to waive it until we are further along.

DR. PAZDUR: A specific example; I won't give you the drug's name, but, for example, got initial approval in lung cancer and, obviously, lung cancer does not occur in children, non-small-cell lung cancer. So it was waived. It is coming in for treatment of brain tumors. We may evoke

obviously then PREA in that situation.

You know, the life history of a drug is not static and usually most people don't just study one indication. Usually, unless a drug is quite specific on a mechanistic level, most of these are going to be explored in multiple indications in adults, which give us ample opportunity to reverse decisions or to not reverse them but to evoke the PREA provision in a more appropriate setting.

DR. LINK: You wouldn't expect the rituximab to be active in ITP, for example.

DR. REAMAN: So, supplemental applications for new indications are also subject to these considerations.

DR. WEISS: Yes. Any new doses formulation or any new indication except a lot of things under PREA because we get lots and lots and lots of supplemental NDA or BLA applications. There are a lot of things that will trigger the Pediatric Rule so that every time you get something in, you have to rethink, you know, and they have to re-request a waiver or deferral, et cetera, every time. S there are ways to, you know, different times to get a bite out of the same apple.

Also, something I guess you mentioned, Mike,

about, you know, you don't know if something is going to be good, potentially useful even if it has been approved, studied for an adult indication.

Under exclusivity, you tend to get a lot of trials, a lot of our sort of templates, in fact, requests are basically to study a broad range of children with relapsed or recurrent solid tumors because you don't exactly know. It's a bit of a fishing expedition and something we will maybe get into a little bit later this afternoon, and something Malcolm raised about, well, how do you make a decision if you have to prioritize.

We have not really been in a position where we will say no. We can actually say--we can not issue a written request. Even if a company wants to come in and request exclusivity, or get ultimately exclusivity, we can basically decide not to issue a written request.

But we rarely do that, because the very same thing; we don't want to miss something that might be good and we don't know and we don't have enough good options anyway in a lot of these recurrent refractory solid tumors. So we tend to say okay, you know, it is a reasonable idea to go ahead and study it.

The likelihood is that you are not going to get a big home run. But you never know until you look and someday we maybe have an embarrassment of riches and have enough options so that we can actually make decisions and say no. But we haven't gotten to that point yet.

DR. D. MURPHY: Just so you will know you have it in your presentation by Dr. Mathis, on her Slide 15, she lists all the things that trigger PREA. So, yes, definitely, it is supplements that come in for any of these five things would trigger PREA.

DR. LINK: Dr. Winick.

DR. WINICK: Thank you. Two questions. First, the discussions that go back and forth, the teleconferences, are timely enough that if Peter has studied a drug and has a limited sampling pattern for doing PK in children, where the numbers are tiny and the drug is also being studied in Europe, that exchange would occur so that they would benefit from Peter's PK? Pardon me?

DR. PAZDUR: Would we necessarily have that material? You know, we have to be in receipt of the material and know about what he is doing and, usually, that is submitted in an NDA process, BLA process, some type of

regulatory submission to an IND.

DR. WINICK: One more comment. It has been asked several times if you have drugs in the same category and you issue a written request and you are afraid not to issue one because you might miss something. But don't the written requests require data gathered in children, correct? So then does it fall to Peter in COG as Chair of New Agents to decide because they have to come to a place to get those children and we still only have a limited number of children.

DR. WEISS: You probably all want to break for lunch. I think this a really good question that maybe there could be further discussion in the afternoon because you are also going to hear Greg and Malcolm talk a little bit, a short presentation, and maybe even Greg Curt from industry can talk.

But for the U.S., for practical purposes, most of the trials are done through COG. There are very few, if any, that are done outside of the Cooperative Group in the U.S. because of, you know, just the whole network is there and the rarity of the diseases.

So, in some ways, for all practical purposes, COG,

you have to bring all of the people to bear at the table, if you will, when you have these discussions and think about what is practical to do.

I think that, you know, with pediatric oncology, may be more than any other disease, I think the industry probably does a lot of work, consulting with their pediatric experts and with representatives from COG to really determine what is feasible.

I mean, again, it is voluntary. You know, we can issue a request and they can decide at the end of the day that it is not feasible, they can ask for modifications, those things can be done, but it has to be sort of a very collaborative sort of process between the regulatory agencies, the industrial partners and the scientific community, in which case, in this case is represented really by the Cooperative Oncology Group.

DR. SANTANA: Just to follow up on that; so when we did the review last year of the ones of pediatric oncology drugs, two-thirds of those studies were conducted in COG or in consortia like BPTC and things like that, and the other one-third were done by the sponsor at whatever institutions they chose, so it's about two-thirds to one-

third historically. I don't know what is happening now but that was the old data.

DR. PAZDUR: And they may elect to do these in Europe. They may elect to do them in South America. We cannot put a restriction on where you do the studies in the sense that the data is meeting U.S. regulatory requirements.

DR. WEISS: In fact, Jean gave a lot of examples over and over again of nasopharyngeal carcinoma. Well, you can kind of guess maybe where those studies are going to be done or are being done.

DR. D. MURPHY: I think that that is a really important point because recently there was an internal review of where the studies are occurring and, as you know, more and more of them are occurring outside of the United States. I don't mean just oncology, I am just talking about overall.

DR. LINK: It is interesting, though, in Dr. Lumpkin's comment, about you have to use your own contextual thing. But, in fact, the context is the FDA reviewing patients who are being taken care of in Brazil. So I am a little disoriented about how, you know, the context of an FDA review is something that was done somewhere else in a

totally different context.

DR. WEISS: It happens all the time.

DR. LINK: I know you do it all the time.

DR. WEISS: It happens in the vaccines world routinely.

DR. LINK: Absolutely.

In deference to taking another bite of the apple, I think it is time for lunch.

Dr. Herold, are you still there?

DR. HEROLD: Yes, I am.

DR. LINK: You are probably taking a break for dinner or something, but we will be back in about an hour.

DR. HEROLD: Thank you. Enjoy.

[Whereupon, at 12:20 p.m., the proceedings were recessed, to be resumed at 1:15 p.m.]

AFTERNOON PROCEEDINGS

[1:15 p.m.]

DR. LINK: The scheduled item on the agenda is our Open Public Hearing. Nicole will give us the background for that.

Open Public Hearing

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of

your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

DR. LINK: We have one individual who has requested to speak, Matthew Alsante representing the Sarcoma Foundation of America.

MR. ALSANTE: I just want to thank you all for giving me this opportunity to speak, and I truly appreciate all the noble work you guys are doing here today and in your

careers. So thank you.

Good afternoon. My name is Matthew Alsante and I am the Executive Director of the Sarcoma Foundation of America, or SFA. The SFA advocates for new and better therapies for children and adults suffering from sarcoma. As everyone here knows, sarcoma is a prevalent pediatric cancer.

Each type of childhood cancer, whether it be childhood leukemia, childhood brain cancer or childhood sarcoma, is an extremely rare cancer group. Thus, we were heartened in November 2005 when the full ODAC met to discuss issues related to post-marketing studies following accelerated approval of products for rare cancers.

On that day, the vexing problems of drug development for very rare populations were discussed at length and scores of suggestions were provided to the FDA as to various types of datasets that would be adequate to determine the efficacy of a product for rare cancer, just in case the numbers were so extraordinarily small that the usual survival studies could not be realistically performed.

Since that meeting in November 2005, however, we in the rare cancer community have not witnessed any

consistent integration of the ODAC advice into the FDA's decisions for oncology products for rare cancer indications.

For example, in October 2006, Novartis obtained full approval for five additional rare cancer indications for Gleevec based on clinical trial data of only a few dozen patients. The approval of Gleevec for these rare cancer indications appeared very much in keeping with the advice and recommendations of the November 2005 ODAC and we heartily applaud FDA for such wise judgment.

However, in mid-2007, FDA reversed course and denied IDM Pharma's NDA for mifamurtide--Junovan despite being supported by overall survival data in several hundred osteosarcoma patients. The osteosarcoma patient community continues to be disappointed that this therapy is not an option for them as they deal with their disease.

In the effort to make progress on these issues, our organization recently filed a Citizen's Petition to FDA to formalize the advice of ODAC in an official Guidance to Industry document. We hope such guidance from FDA will manifest in a clearer pathway for an industry sponsor to take when seeking a rare cancer indication.

In light of the FDA's accelerated approval process

and challenges inherent in the research and development of treatments for rare cancers, the question is ultimately about what evidence will support approval for treatments for rare cancers and how FDA can accommodate such treatments under its current authority, regulations, or enforcement policies.

We believe that the overall message from the ODAC meeting nearly two years ago was a resounding call for a change in the status quo. The Sarcoma Foundation of America supports the ODAC's recommendations and advice of November 2005 and, hopefully, that this gathering of the ODAC Pediatric Subcommittee reiterates its support for special consideration for the exceptional situation of developing new drugs for rare cancers such as pediatric cancers.

We would request that in your deliberations today, you discuss how to make progress on global policies that would help get more weapons into the hands of oncologists who treat rare childhood cancers.

Thank you for your time and attention to this matter.

DR. LINK: Thank you very much.

We will now proceed with a couple of the

presentations for the afternoon. First, Dr. Malcolm Smith from CTEP talking about how we prioritize new agents for pediatric oncology.

Prioritization of New Agents in Pediatric Oncology: A Perspective from CTEP/NCI

DR. SMITH: I will be talking about prioritizing new agents in the pediatric oncology setting. I did take the red eye back from AACR last night, along with Dr. Curt, so if I say anything really stupid, just please attribute it to sleep deprivation and not to something else.

[Slide.]

When Karen asked me about this, I thought I think I have done this before. This is a slide from nine years ago, here at this FDA/ODAC meeting I think or Pediatric/ODAC, and talking about how do we prioritize agents for children with cancer.

This was I think right before the Phase 1 presentation of Gleevec at ASCO, so it was right at the foot of a new era, and how far we have come in those nine years since this.

[Slide.]

So, why is this I think the most important task we

have? Well, the old ways that have improved outcome just aren't sufficient anymore. We can't give more therapy and so, as one of the slides showed earlier, we have really reached a plateau in improving mortality.

Something that I think is really an important concept is the opportunity costs of picking the wrong new agents for definitive evaluations. It is fine to say we want to study lots of new agents in the pediatric setting, but there is an opportunity cost if we pick one of those agents and because of that we haven't picked the one that was really effective.

There are obvious costs to the individual patient for not getting an effective treatment, and then really the loss of 5 to 10 years of opportunity for improving outcome because our cycles for drug development are about 5 years long from a Phase 3 trial.

[Slide.]

Just to make that point, when we come into a Phase 3 trial for a Ewing sarcoma or a neuroblastoma or a rhabdomyosarcoma, we are basically talking about something that is going to keep us busy for the next five or six years. If we pick the right agent to study, if we have made

good prioritization decisions, we might have a chance of improving outcome. If we picked an ineffective agent, then, no matter how well this trial is done, we may learn something but we want to improve outcome.

[Slide.]

Why so challenging? Well, we have talked about small numbers of patients, we can't do very many Phase 2 trials like in breast cancer where you may be able to do dozens of Phase 2 trials in a year.

The menu of agents is very large and is primarily driven by adult cancer drug development. Most agents do have some rationale for studying in one or more pediatric cancers. But, to this point, often the data are fragmentary. There is a little data here, a little data there, and we really don't have a global picture of the information that we would need for the most effective prioritization.

No uniform standards for prioritizing agents for evaluation.

[Slide.]

This is a list of agents that we have studied in children. You can multiply this list by two or three for

all the agents that were EGFR targeted that we haven't studied, and add another, double it again, and agents that are in the preclinical setting that are different targets than the ones listed here that we just haven't gotten to yet.

So, more than we could ever hope to study against any group of childhood cancers.

[Slide.]

The concept I would like to focus on is how to keep our pediatric drug development child focused. We have agents developed by pharmaceutical sponsors for adult cancers that may or may not have relevance in the pediatric setting.

You know, the EGFR inhibitors, HER2 inhibitors, experience to date suggests very limited applicability in the pediatric setting. It is unclear whether VEGFR targeted therapies will have the same applicability in the pediatric setting as in the adult setting, but these are the agents that companies are focusing on.

So, the hypothesis would be that a more systematic preclinical data-driven prioritization process for introducing novel agents into the pediatric oncology setting

may help to ensure that selection of agents for pediatric evaluations remains a child-focused process driven by the needs of children and really distinct from the needs of particular sponsors who are developing an agent for adult indications.

[Slide.]

So, the things that I can add to the list that weren't on the 1999 list, you know, we are much more sophisticated now in terms of assessing RNA and protein expression for targets.

Genetic models for childhood cancers that can really define oncogenic roles for putative targets--and even if something may not be a target itself, there may be a synthetic lethal relationship between the new agent and the genetic lesion for a particular childhood cancer.

Genetic evidence in preclinical models for the oncogenic role.

This is the kind of biology data, the array based methods. At AACR this year, there were a number of advances in the pediatric setting reported and I will give a couple of examples of those.

The other areas are to show that the agent

directed against the target show in vitro activity within relevant concentration ranges in appropriate cell line models.

Then, the agents show in vivo activity against relevant pediatric preclinical models.

Still at the list in terms of prioritization would be the agent's activity in adults. That could still be something that would sway us, but also the number of agents in the class that have already been studied.

I would say that once we have hit 3 or 4 VEGFR-2 inhibitors, if that many, I am not sure how many we need in order to evaluate that in the pediatric oncology setting.

It may not be something that FDA can help us with. But, as a research community, that is something that we need to address.

[Slide.]

An example. This whole process is feasible and the IGF-1 receptor in Ewing sarcoma back in 1990, showing that IGF-1 receptor expression, IGF-1 expression, also the receptor is common in Ewing sarcoma.

[Slide.]

Then, Jeff Toretsky and Lee Hellman's group showed

genetically that the IGF-1 receptor was required for transformation by the EWS/Fli-1 fusion gene. You can make dominant negative mutants of the IGF-1 receptor. This was done a year or two later. These not only inhibit tumorigenesis, induce apoptosis, but increase chemosensitivity and then a small molecule inhibitor, the IGF-1 receptor, slows tumor growth in Ewing sarcoma and other childhood sarcomas.

[Slide.]

Again proof of principle here is from our preclinical testing program. Again, here, we are not going to look at 6 or 7 IGF-1 receptors but we will look at one target as proof of principle.

You can see good regression with a Ewing sarcoma xenograft. In the middle panel, the control line shown in gray, the control animals, the tumor grows quickly. The treated animals, the tumor's slow regress during the course of treatment.

So, proof of principle from the expression through the genetics, through taking clinical agents and showing their effect in relevant in vivo models.

This is a process, a data-driven process. I will

in fairness say it didn't hurt that responses were seen in the Phase 1 trials, you know, the IGF-1 receptors fairly early on, and this is really stimulating this class of agents development.

[Slide.]

The kind of advances in AACR, and these advances come more and more quickly in terms of understanding the biology of different childhood cancers. So one report, a late-breaking abstract at AACR showing the pilocytic astrocytomas; most of these pilocytic astrocytomas have a novel rearrangement that produces an in-frame fusion gene that is an activating fusion protein and so B-Raf is activated in these tumors.

The fusion has constitutive kinase activity.

This changes rather dramatically our understanding of this particular childhood brain tumor.

[Slide.]

Another discovery reported at AACR, wanted to attend the session, one of the reasons I needed to take the red eye was the identification of ALK as the major neuroblastoma predisposition gene.

Heritable mutations in the kinase domain of the

ALK proto-oncogene, the major genetic determinants of familial neuroblastoma. It is not just familial neuroblastoma, about 10 percent of sporadic cases also show activating mutations in ALK.

So, again, we have data here that really could change the way we might approach the treatment of this relatively small subset of patients with neuroblastoma.

[Slide.]

Now, to focus, give a couple more examples of in vitro activity and in vivo activity of the clinical agents and relevant preclinical models.

One point is setting the bar well when you are looking at preclinical data. I don't know how many times I have read papers that significant activity and to the clinicians in the room it's progressive disease. So there is a treatment effect but in a patient we would not probably consider it clinically significant.

[Slide.]

This is a very nice paper and I don't mean to pick on it, but there is a significant difference in the Kaplan-Meier curve for these GBM xenografts that were treated with I think it was erlotnib, but again this is a significant

difference. But does this mean, would this make us prioritize this agent for evaluations in pediatric gliomas.

So setting an appropriate bar, a significant difference in EFS distribution or in the Kaplan-Meier curves in these preclinical experiments. There is a low bar and progressive disease with relatively modest growth delay often meets that bar.

A much more relevant bar in the pediatric oncology setting is tumor regression. I mean, that is the agents that we use, were really selected on the basis of their ability to induce regressions.

[Slide.]

If you look in the middle panel there, the relative tumor volumes, this is vincristine, rhabdomyosarcoma xenografts at the top, vincristine and ALL at the bottom, again from our preclinical testing program.

We like to see agents like this. And if we see them against a tumor panel, then, it stimulates interest in the agent. Cyclophosphamide, this is again from one of our first papers by the Pediatric Preclinical Testing Program.

The map on the right side shows the responses to all the xenografts that we tested--ALL, osteoneuroblastoma,

rhabdomyosarcoma, Wilm's, cyclophosphamide being highly active, maintain complete responses in many of the xenografts.

Ideally, these are the type of activity or at least in selected panels that we would like to see for other agents that we are testing. So, in fact, we have observed comparable activity for several novel agents that we are testing in our in vivo and in vitro preclinical testing program.

These observations of high level activity against one or more panels, good tumor regression is really stimulating both to the company and pediatric Phase 1 investigators and disease committee leaders to move these agents quickly into the pediatric setting.

I will be glad to say more about that in questions.

[Slide.]

One point is that the preclinical data that might be available for combinations for evaluation, it is pretty common for people to say, well, we didn't see single-agent activity, so we will use it in combination.

That may be a good thing to do but, if it wasn't

active as a single agent, you really need good evidence that it is doing something in combination distinctive, far beyond what it was doing as a single agent. There is some favorable interaction.

So, in terms of combinations, you know, if you have got single agent activity, then, like our standard approach is to add it to standard agents, maybe to novel agents. So that part is easy.

What if the agent has limited single agent activity? What you would really like to see is preclinical demonstration of potentiation of activity of standard agents or of novel agents. When you put them together, you see a good potentiation.

Again, an example from the preclinical testing program.

[Slide.]

This is a combination treatment with rapamycin and cytoxan in some rhabdomyosarcoma xenografts. The top is cytoxan, the bottom is vincristine. Rapamycin by itself, modest activity, certainly no regressions. Cyclophosphamide, again, an active agent causing regressions. But the combination together causes marked

complete regressions that are maintained through the 12 weeks of treatment and observation.

So, it's not just cyclophosphamide that this effect was observed for. Again vincristine and rapamycin--this is half-dose vincristine, very little activity. But then the combination shows substantial activity and, when vincristine is used at full dose, you see maintain complete responses.

You would really like to see data similar to this showing some kind of potentiation of the effect of the agent. Even though it wasn't particularly effective as a single agent, that it was effective in combination.

[Slide.]

The final point then on this list is the adult activity of the agent. A number of agents in class are already being studied in the pediatric setting. So, if an agent is highly effective in a particular cancer, depending on the biology of the cancer and the agent, there may be enthusiasm for moving the agent into a pediatric evaluation simply based on that.

But again the number of VEGFR-2 inhibitors we need to study, the number of Met kinase inhibitors, there is a

limit to how much we can do because, again, there is any opportunity cost. Studying one of those prevents us from studying something else that may be in fact more effective.

[Slide.]

So, this was the final two slides here before the summary. What are we prioritizing for? Again, this was from nine years ago.

[Slide.]

Basically, there is a drug development pyramid where, at the base, the Phase 1 studies, we can do a lot of Phase 1 studies. We can do fewer Phase 2 studies and then we can do very few Phase 3 studies.

Again, I showed earlier that one study every five years or so. So, when we are prioritizing, part of the issue is to be clear about are we prioritizing for Phase 1? That bar may be relatively low because we can do a lot of studies. But, once we get past Phase 1, it is much more challenging and certainly getting to Phase 3, you know, the prioritization process needs to be very stringent at that point.

[Slide.]

The niches then that we could prioritize for--and,

again, when we are prioritizing, what groups of patients will we be prioritizing these agents to study in?

The multiple relapsed patients Phase 1, single agent Phase 2, multi-agent Phase 2.

First recurrence or second recurrence, we generally do pilot studies, multi-agent combinations, single agent comparison to historical control when we have that, randomized studies with either a selection, pick the winner design, or a screening design.

There is a potential in this first recurrence or second recurrence setting for single agent window evaluation prior to the multi-agent therapy.

Another niche is the newly diagnosed, metastatic patients. These many times are osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, the outcome is quite guarded. There are relatively small numbers of patients but it is a chance to pilot novel treatment approaches that may then be moved into the newly diagnosed setting.

In the sarcoma world, it would be localized tumors. We are talking about only 50 to 150 patients per year and again one or two studies per decade that we may be able to do for each diagnosis.

[Slide.]

To end, again I will posit that we are in a position now to really apply a more systematic preclinical data-driven process to help ensure that as we select these agents, we really are doing it in a way that is focused on the population that we want to benefit.

The relevant data; I mentioned before, we have the tools to do all of these now in terms of expression of RNA protein, genetic models, the preclinical in vivo/in vitro models and then, by assembling the relevant preclinical data sets for agents that are entering pediatric evaluation today--I mean, this is all in many ways an experiment.

But, by assembling this data set and learning from these data sets, we should be able to refine this prioritization process and improve it in the coming years.

So, that was all I had.

Clarifying Questions from the Committee

DR. S. MURPHY: Thank you, Malcolm.

I have a question. I mean, having observed the development of the pediatric preclinical testing program over the years and seeing it mature, one thing is that, yes, we have the tools now and we have some kinds of bars that we

could set to think what is promising or not. But I guess I have a question about feasibility because there are so many drugs, so many possible targets, it's just like so many genes.

I wonder what is the capacity of your panel in terms of both numbers of agents that you can put through the panel and that is, of course, limited by time and money and people and, surely, those are not unlimited.

So, that is one question I have is how do you, in a sense, prioritize what you are going to test. I mean, initially, you spent quite a bit of time, I know, importantly testing agents that we know work, like cyclophosphamide and vincristine. And now you are moving on toward, you know, agents that have numbers and letters for their names, which is a good sign, but have you yet identified from this exercise something that you are ready to say, aha, that is the one next to put in a Phase 1 trial.

That is what I want to know, and where, and what is really your throughput.

DR. SMITH: There are several things to say. The throughput is about 10 to 12 per year and most of the agents that we have tested we are up to about 30-plus agents now