DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

Wednesday, April 16, 2008

8:30 a.m.

C O N T E N T S

PARTICIPANTS

Michael Link, M.D., Acting Chair
Nicole Vesely, Pharm.D., Designated Federal Official

ONCOLOGY DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Michael Link, M.D.
Ronald Richardson, M.D.

INDUSTRY REPRESENTATIVE (Non-Voting)

Gregory Curt, M.D.

TEMPORARY VOTING MEMBERS

Peter Adamson, M.D.
Susan Blaney, M.D.
Kenneth Cohen, M.D., MBA
Jerry Finklestein, M.D., C.M.
Melissa Hudson, M.D.
Sharon Murphy, M.D.
Angela Myers, M.D., Patient Representative
Gregory Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Cindy Schwartz, M.D.
Malcolm Smith, M.D., Ph.D.
Elaine Vining, Consumer Representative
Naomi Winick, M.D.
Victor Santana, M.D.

FDA (Non-Voting)

Murray Lumpkin, M.D., M.Sc.
Dianne Murphy, M.D.
Richard Pazdur, M.D.
Karen Weiss, M.D.

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. LINK: Welcome to the Pediatric Oncology Subcommittee of ODAC. We have a meeting this morning where we are going to consider and discuss opportunities for enhancing global pediatric oncology drug development and expanding international regulatory interactions given the January 2007 legislation introduced in the European Union that governs the development and authorization of medicines for use in children aged 0 to 17 years.

This is going to be an educational session for us. We will learn from our European colleagues and hopefully foster some easier collaborations internationally.

Welcome. Perhaps we can go around the room and introduce everybody who is here, perhaps starting with Dr. Adamson on the end there.

DR. ADAMSON: Peter Adamson, Children's Hospital of Philadelphia.

DR. HUDSON: Melissa Hudson, St. Jude Children's Research Hospital.

DR. WINICK: Naomi Winick, UT Southwestern, Children's Medical Center.

DR. SCHWARTZ: Cindy Schwartz, Brown University, Providence, Rhode Island.

DR. SANTANA: Victor Santana from St. Jude Children's Hospital in Memphis.

DR. FINKLESTEIN: Jerry Finklestein from Long Beach, California.

MS. VINING: Elaine Vining. I am the consumer rep for the Pediatric Advisory Committee of the FDA.

DR. BLANEY: Susan Blaney, Texas Children's Cancer Center, Houston.

DR. LINK: I am Michael Link from Stanford.

DR. VESELY: Nicole Vesely, Designated Federal Official, ODAC.

DR. RICHARDSON: Ron Richardson. I am the token medical oncologist from Mayo Clinic, Rochester, Minnesota.

DR. REAMAN: I am Gregory Reaman, Children's National Medical Center, Children's Oncology Group.

DR. S. MURPHY: I am Sharon Murphy at the University of Texas Health Science Center in San Antonio, Children's Cancer Research Institute, Director there.

DR. LUMPKIN: Good morning. I am Murray Lumpkin. I am the Deputy Commissioner here at FDA for International

and Special Programs.

DR. D. MURPHY: I am Dianne Murphy, another Murphy, here at FDA in the Office of Pediatric Therapeutics.

DR. WEISS: Hi. I am Karen Weiss, Deputy Director of the Office of Oncology Drug Products at FDA.

DR. PAZDUR: Richard Pazdur, Director, Office of Oncology Drug Products, FDA.

DR. CURT: I am Greg Curt. I am Ron's backup as a medical oncologist, AstraZeneca Oncology, the industry representative to ODAC.

DR. MYERS: Angela Myers, Children's Mercy Hospital in Kansas City.

DR. LINK: We also have on the phone, Dr. Ralf Herold. Are you there?

[No response.]

DR. LINK: Dr. Saint-Raymond, who is the head of Scientific Advice and Orphan Drugs from EMEA.

Everybody has to remember that in order for people on the phone to hear, and in order for our transcriber to hear, you have to use your microphone. So please remember to push the top button before you talk.

Conflict of Interest Statement

DR. VESELY: The following announcement addresses the issue of conflict of interest with respect to the meeting and is made part of the public record to preclude even the appearance of such at the meeting.

The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee will consider and discuss opportunities for enhancing global pediatric oncology drug development and expanding international regulatory interactions given the January 2007 legislation introduced in the European Union that governs the development and authorization of medicines for use in children aged 0 to 17 years.

Based on the submitted agenda for the meeting, it has been determined that this meeting is being held for educational purposes and all interests in the firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting.

Dr. Gregory Curt is serving as the industry representative, acting on behalf of all regulated industry, and is employed by AstraZeneca.

We would like to remind members and consultants that if the discussions involve any products or firms not

already on the agenda for which an FDA or government participant has a financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

Thank you.

DR. LINK: Dr. Herold, is that you on the phone?

DR. HEROLD: Yes, thanks. Good morning to you all.

DR. LINK: Thank you. Remind us that you are there sometimes, because it is very difficult to see. But, if you need to talk, please, just interrupt us.

I have been asked by Dr. Finklestein, who wants to give just a very short comment before we begin, so I will yield the floor to my esteemed senior colleague from the great State of California.

DR. FINKLESTEIN: Thank you, Mr. Chairman.

I have the advantage of sitting beside Elaine Vining and looking diagonally over to Dr. Murray also known as Mac Lumpkin. Ten years ago in pediatric oncology, we were very frustrated because we felt that we weren't being heard in trying to develop new drugs for our children with oncologic disorders.

Elaine was at the American Academy of Pediatrics and called a meeting. A number of you were at that meeting including Dr. Pazdur--Karen, I am not sure whether you were there, I think you were. I think Dianne Murphy was there, and Mac Lumpkin was there and there were representatives from Pharma, and we were frustrated.

Mac said hold on and all of a sudden he took the FDA people to another room and all we could see through the glass was they were working on some kind of blackboard presentation. And I was co-chair of the meeting.

Mac came back and said we can do this. He outlined a plan for conversation, negotiations and working together. In some respects, this meeting, 10 years later and all the meetings for the past several years, is a reflection of the tremendous leadership of Dr. Lumpkin. I acknowledge you and the individuals who met that day, 10 years ago, under your auspices.

Thank you, Mr. Chairman.

DR. LINK: Be it resolved.

Anyway, so we will now proceed with the regular items on the agenda beginning with Dr. Weiss, who will introduce our topic.

Opening Remarks

DR. WEISS: I can't top what Dr. Finklestein just did, so I just want to welcome you all to this meeting and to a beautiful spring day in the D.C. area. I know that many of you actually took the red eye here from AACR and I truly appreciate that you elected to be here at this meeting.

This is billed primarily as an educational session. Europeans have just recently enacted their legislation that is somewhat patterned and modeled after the U.S. legislation. So we thought this was an appropriate time to hear what that is all about so that perhaps this would be a good avenue to even further expand and harmonize across both sides of the Atlantic to improve outcomes of pediatric data for children with cancer.

There are times during the agenda for breaks where we hope that you will have questions that the people that are experts here can answer for you.

I don't have formal questions for the committee unlike previous meetings because I want this to be more of a dialogue and an interactive session. We want to just exchange things on both sides and, hopefully, at the end of

the day, just have a better understanding of how to move the field forward.

But before we get into the whole foray of international development, Dr. Lisa Mathis, from the Office of New Drugs and the Associate Director for Pediatric and Maternal Health Staff, is going to basically update everybody on what is new with pediatric legislation since the passage of the FDAAA, or FD Triple A, Act just recently.

DR. LINK: Of course, I hope everybody has read the entire FDAAA thing that was distributed to you. It was wonderful reading.

Brief Overview FDAAA

DR. MATHIS: Good morning and thanks for the introduction.

[Slide.]

If you didn't have time to read the entire Act, I will try and summarize some of the more relevant points for you.

[Slide.]

These are just acronyms.

[Slide.]

We are going to go over a brief overview of the

pediatric history at the FDA. Then, I am going to go over the major changes to both Title V, which is the Best Pharmaceuticals for Children Act of 2007, as well as Title IV, which is the Pediatric Research Equity Act.

[Slide.]

This is just a brief overview of all the laws that have been passed in the last 20 years to help us with pediatric drug development. Now, I always do really complain that I have to give the dry regulatory talk when everybody else gives all the fun data, but this stuff is pretty exciting.

We have made a lot of advances in pediatric research because of this Act. We have developed an infrastructure and we have really taught people that it's okay to study pediatric patients, so that way they can have the same level of evidence-based care that adults have had for years.

Really, so much of this started in the late '70s with the labeling requirement where the FDA required the Pediatric Section of labeling and asked drug companies to submit evidence that was out there, that they had not previously submitted to the agency to include in labeling.

Of course, this was not much success, so that increased the efforts by the FDA and other advocates, such as the American Academy of Pediatrics and other interested parties, to really start working on getting more information for pediatric patients.

In 1994, there another labeling rule. But the big stuff came in 1997, with the passage of the FDA Modernization Act and the inclusion of an incentive program for drug companies to study pediatric patients.

Of course, you know that they got marketing exclusivity. So, if the companies did the study that was requested by the FDA, then they got six months of marketing exclusivity which, in essence, blocks generic drugs. And it was a big financial incentive for them to study pediatric patients.

Because pediatric patients, especially oncology pediatric patients are so few relative to the number of adult patients, there wasn't a whole lot of financial incentive for companies to study them previously. So this has really increased a lot of the research that has been done.

In 1998, we had the Pediatric Rule, which was a

rule by the FDA that if a drug was anticipated to be used in pediatric patients, then, companies were required to study pediatric patients.

In 2002, we had the Best Pharmaceuticals for Children Act, which reauthorized the incentive program under FDAMA. In 2002, we also had our Pediatric Rule enjoined. The Court said that we could not require drug companies to study pediatric patients.

Fortunately, in 2003, the Pediatric Research Equity Act passed, which codified the FDA's authority to require studies for pediatric patients.

Now, in 2007, we have had FDAAA or the Food and Drug Administration Amendments Act of 2007 where both PREA and BPCA were reauthorized. They also included medical devices in this and Dianne Murphy has been working a lot with CDRH. So they are going to be working a lot, working on medical devices for pediatric patients, which is also a huge thing and very difficult to do.

[Slide.]

I put this slide up here to remind us that despite how much progress we have actually made in pediatric research, there is still a whole lot more to go. This is

actually one of Malcolm Smith's slides, and it was very striking to me because you can see this is childhood cancer mortality. Although the rate has come down dramatically, we have certainly leveled off in our progress. And there is still a lot more work that needs to be done.

So I just put this in here to remind us that no matter how much success we have had, we have yet to conquer the problem of pediatric oncology.

[Slide.]

I am going to start by going over some relevant changes to the Best Pharmaceuticals for Children Act.

[Slide.]

This is just a side-by-side table. The improvements include extending this committee to 2012 and also a statement that this committee can make recommendations directly to the Internal Review Committee, which I will be reviewing in a few minutes in the implementation of the Best Pharmaceuticals for Children Act.

The new BPCA also expands the role of NIH to include all pediatric therapeutics, not just drugs. Before, the NIH was only involved at the level of off-patent drugs.

[Slide.]

The Internal Review Committee was established under the Best Pharmaceuticals for Children Act 2007 to provide oversight to required and requested pediatric activities within both CBER and CDER.

There is expertise that is mandated in the law so we have to have people from the Office of Pediatric Therapeutics, ethicists and also subject matter experts.

We have a pediatric oncologist that sits on this committee. Really, the hope is that this group will be able to provide consistency and quality in both the written requests and the required studies under both BPCA and PREA.

[Slide.]

The National Institutes of Health have an expanded role. They have always had to make that list of priority off-patent drugs that need to be studied in pediatric patients and then they go through the process of letting grants and contracts to get those studies done.

Previously, it was only off-patent drugs that they did this for, but now there is actually an expansion and they get to address all pediatric therapeutics. This becomes very important because of the biologics. As you all know, biologics are certainly taking a larger role in the

treatment of cancer.

They will be having a meeting in June and July of 2008. It sounds like a long meeting, but it is not. It is the very last day of June and the first day of July.

The law does require consideration of available information on drugs and biologics, so we are supposed to look at the body of evidence that is out there existing in probably adult patients, as well as small clinical trials in pediatrics, and then we will move forward with NIH's help and NCI, I am sure, in trying to get some more drugs developed for pediatric oncology patients.

[Slide.]

Other improvements to the Best Pharmaceuticals for Children Act. It still only works for drugs, so BPCA does not extend to biologics except where NIH is concerned.

The studies are still voluntary and it still applies to the entire active moiety. The written requests may now include both on-label and off-label indications. Before, we had to choose, which limited our options for what we could ask for in the studies, and the written requests may still be issued for orphan indications.

Now we can ask for preclinical studies as a term

of the written request. Previously, we were limited to only asking for studies in pediatric patients, so this really extends what we can require as part of the written request as far as both animal or other preclinical studies.

I should note that the law certainly doesn't allow us to only ask for preclinical studies. It is preclinical studies plus then clinical studies.

There is a priority review for all applications. Now, I don't think that that would really affect oncology products very much because, obviously, as a life-threatening condition, these generally get priority review status anyway. But that is a six-month clock versus a 10-month clock for review and decision about whether or not to approve.

[Slide.]

This again goes over the preclinical studies. As I said, the law does not allow for preclinical studies only, but this is really something that I think that we could use to the advantage of pediatric oncology patients to include nonclinical studies in the written request.

[Slide.]

The other things that we are doing now with BPCA

2007 is that all adverse events must be submitted with the application. This allows us to have a much more extensive and efficient safety review of the product. There was no requirement to do this previously.

We have 6 months to review the studies and determine if the terms of the written request were met. Previously, we only had 3 months, which meant that we hadn't been able to dig all the way through the data that had been submitted and, on a few occasions--not very many, but a few--by the time that we had done the thorough review, we found that the studies had come up short of what we would have expected the sponsor to do.

On face, they looked like they met the terms. But, as we got deep into the data, we found out that they did not. So in a couple of cases, the drug companies had gotten pediatric exclusivity when, if we had had time to go through the entirety of the data, we would have probably come down with a different decision about granting exclusivity.

So this again makes it just more incentive for the drug companies to do very good studies in pediatric patients.

Then, the other thing is that the companies have to have 9 months of exclusivity at the time that we make the determination.

This important because previously, the drug companies used to be able to submit their studies the day before their patent or exclusivity expired and so, given that we had 3 months to look at that data and figure out if they met the terms of the written request, there were a couple of times when companies who didn't meet the terms got that 3 months de facto exclusivity while we were trying to figure out whether the terms had been met. So this protects us from that happening.

In addition, the written requests will now become public and this is really good. Previously, they were commercial confidential, so now everybody can see what we asked for and what was done. Studies that were performed must be added to labeling whether they were positive or negative or inconclusive. There has to be now wording in the labeling that provides the public with some information about what was done and what we found.

Before, there was no labeling requirement and even though the FDA had certainly moved towards trying to include

this information in labeling, because it really is our one shot to get studies in pediatric patients, that did not always happen. Now it must.

The full reviews are also posted, so now you will have both the written request plus detailed information about what was done in the studies and how the FDA actually evaluated those studies.

We will also have an adverse event review for pediatrics, which is the same as we have always done. The Office of Pediatric Therapeutics is in charge of the Pediatric Advisory Committee and previously, a year after exclusivity was granted, they reviewed all the pediatric adverse events. They did that in the context of all adverse events in both pediatrics and adults. Now this will be done a year after labeling.

We actually think this will help because, if you remember, the exclusivity used to happen at 90 days or three months with the approval happening in 6 to 10 months. So it is possible that we were missing a pretty big gap of pediatric use because there was a gap in between the time that the exclusivity was granted and the time that a drug was approved. So we may have lost some information in that

time frame. We won't do that anymore.

I did put on here a little note that the sunset for PREA and BPCA is October 1st, 2012 so, for people who are interested in the reauthorization, you can start thinking now about ways that we can improve it for the next rounds and we will keep our fingers crossed that we do get a next shot at this.

[Slide.]

Now, I will go over the changes to the Pediatric Research Equity Act of 2007. I should note that I am not going to go through all my backups but, in my backups, I did similar side-by-side tables for all the things that changed in BPCA and PREA. But I am only covering those things which I thought really impacted this group.

[Slide.]

The improvements for PREA. The basics stay the same. PREA is the mandatory program where studies are required and it applies to both the drugs and biologics. Studies for orphan indications are exempt, and required studies are only for the drug or indication that is currently under review.

You know this has been a little bit of an issue

for this particular patient population because obviously, most of the oncology products that come in for adults are for adult cancers and pediatric patients are very different, so we oftentimes cannot mandate that the company study the oncology products in children.

[Slide.]

These are the applications that will trigger PREA, so those are applications that come in with new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

Of course, as I mentioned earlier, when the indication is prostate cancer or breast cancer, colon cancer, cancers that don't happen in significant numbers in pediatric patients, it really limits the scope of the required studies that we can ask for.

That is why the Best Pharmaceuticals for Children Act has been so important for pediatric cancer.

[Slide.]

We have been able to apply PREA for a couple of indications and we can certainly see PREA being useful to the pediatric population in the oncology spectrum for leukemias and lymphomas, as well as for supportive care, and

there have actually been a couple of examples.

This is a more recent one. Of course, we have the anti-emetics and other products that have also been studied under PREA, but this is a more recent one. I gave you the list last time of the older ones. I didn't want to bore you.

[Slide.]

As far as an age appropriate formulation, again, for oncology products, a lot of times this isn't too relevant because a lot of them are intravenous. But the drug company, if they make an oral formulation, does have to make a formulation that a pediatric patient can take. So, under 6, some sort of liquid formulation; older than 6, a smaller tablet.

Again, the study results must be included in labeling as they are in the Best Pharmaceuticals for Children Act.

The full reviews are posted. This is new, so the public will be able to look at what studies were performed and what the FDA's analysis of those studies and the conclusions of the studies, as well. Then the pediatric adverse events will be reviewed by the Pediatric Advisory

Committee, very similar to what was done under the Best Pharmaceuticals for Children Act for the last five years.

I am going to put on here the sunset again. So if you all can think of any ways to improve this piece of legislation, now is the time to really start thinking about that.

[Slide.]

In conclusion, the reauthorization did provide for continued incentive and requirements for pediatric studies and pediatric oncology still plays a major role in the new legislation.

But despite the progress in pediatric oncology drug development specifically, improvements in the survival rates have slowed.

Scientists in every sector must collaborate using the tools available to them, including this legislation, to provide new opportunities for treatment, and we really hope to be able to use this legislation to improve collaborations between all interested parties.

I am now to ask for questions, is that correct?

DR. WEISS: We just thought that if there are clarification questions regarding FDAAA or any aspects of

PREA and BPCA, Lisa is the best person to answer them, or even give her your suggestions for 2012 if you have any at the moment, that would be great.

Clarification Questions from Committee

DR. SANTANA: So, Lisa, can you, since you opened up the door for the reauthorization process, can you review with us what is the internal process that occurs in terms of seeking out the different stakeholders to get information that you guys then use internally to make recommendations to Congress?

Then a subquestion to that is how can this committee get involved in that process.

DR. MATHIS: Well, the new legislation certainly does give this committee authority to talk directly to the FDA and make recommendations, so I will tell you that that opportunity exists in the legislation.

It would be there anyway. I mean, obviously, we take your recommendations very seriously. The internal process for looking--what we had to do for the last reauthorization was to really do a retrospective look at what we had done.

The GAO actually did a report and we worked with

them on that. And, during that process, we certainly did learn a lot about ways that we could improve the process. We talked with the GAO about the shortcomings of process and where we felt like things could be improved. But, as far as making recommendations to Congress, we are part of the executive branch so we can't do that directly.

We did have the benefit of having interested parties like the American Academy of Pediatrics that worked with stakeholders and I would say that, outside of this group, working directly with the FDA, it would be very helpful for NCI and other people who were interested in these matters to work with the American Academy of Pediatrics.

They were fabulous at talking with stakeholders and really trying to make improvements in the law that would benefit children. So we could certainly facilitate you all getting in touch with them. We know the people that were involved and I would be happy to do that.

Elaine Vining was actually with the American Academy of Pediatrics and probably Dr. Lumpkin may have some insight, as well--because they were at higher levels, that worked with the GAO and tried to sort out what we had done

right and what we had fallen short of with the last set of legislation.

MS. VINING: One comment that I just wanted to share was that, during the reauthorization, this most recent reauthorization, one of the efforts that was underway and fought hard for but did not actually come to pass was making PREA permanent. And we are hopeful that, in the future, we can make PREA permanent so that children can be on the same level footing for therapeutics as adults are.

I don't know if there is something that this subcommittee and perhaps other FDA subcommittees might want to raise to FDA as a voice that could in the future make sure that there is a strong effort to get PREA reauthorized in 2012 and make it permanent. That is one effort that I think we are very eager to see happen.

DR. CURT: I think the new requirement for placing studies on the label certainly provides for more transparency under the new PREA requirements, but pediatric indications are a different issue.

One of the things that would be interesting to know is what level of evidence would be required for a new pediatric indication in a disease where you may have

difficulty doing a large Phase 3 trial and your judgment will be based on a robust Phase 2.

So pediatric indications based on what level of evidence in Phase 2 trials in the absence of being able to do a Phase 3 trial just because of logistics.

DR. MATHIS: With other conditions we are often able to extrapolate from adequate and well-controlled trials in adults supported by smaller studies in pediatric patients. But again, in this case, because we generally don't have adequate and well-controlled studies for the same types of cancers in adults, we cannot extrapolate.

A lot of times this comes down really to a review decision, and perhaps I will defer to Dr. Weiss to answer this question.

DR. WEISS: I think just to comment, too, that a lot of people I think at this table and in this room are familiar with is that even in the adult setting where there are many more patients, in oncology, we do make approval decisions based on Phase 2 type studies.

It is hard to give a very specific thing because it is really going to depend on a lot of prior experience and how much you can borrow from other bits of information,

but I would have to say that in oncology in particular, Phase 2 is probably not as unusual as in some of the other more common settings.

DR. CURT: I don't know the answer to this, but has Phase 2 data been used to provide new pediatric indications?

DR. WEISS: Yes.

DR. MATHIS: I will add, too, that some time ago this committee actually had input with the Oncology Group about the type of written requests that would be issued for cancer in pediatric patients and, once all the written requests become public, you will certainly be privy to the difference between what we asked for in the oncology written requests versus other written requests.

Other written requests, we often ask for very large trials and in oncology we ask for more Phase 1, Phase 2 studies because again that's the only option that we have.

DR. REAMAN: Just to follow up on Elaine's point about permanent authorization of PREA and, given its limited applicability to the pediatric population in oncology, does permanent authorization preclude changing it at some point in the future, specifically, the requirement for same

indication in the adult and pediatric populations, do you know?

DR. MATHIS: I do not think so. But I would have to defer to people with more legislative experience.

MS. VINING: I can perhaps shed some light on that. No, it does not preclude that. It would be permanent and it could be revised when necessary and when something came up.

It just keeps it on a level playing field and every five years it doesn't have to come up for reauthorization.

DR. WEISS: At one of our prior meetings, we also talked about how we are defining cancer anyway and perhaps some time in the not too distant future, when we can understand things at are more molecular or targeted level, there might be better ways to extrapolate adult data and adult tumors to pediatric tumors based on sort of mechanistic pathways, in which case PREA would hopefully become more relevant.

DR. LINK: Assuming we know that the drug targeting that pathway is actually the mechanism of how it beats the cancer.

That was a great summary, but I wanted to know, having a long plane ride I actually read a lot of this stuff--so could you talk a little bit about the Pediatric Advisory Committee especially, if you can, sort of give us a heads up in terms of how it functions and especially related to how it is different in the EMEA, you know, because they had sort of a similar thing, that would help.

DR. MATHIS: Again, since Dianne Murphy is back at the table, the Pediatric Advisory Committee is actually hers, so I will let her let you know all the details about that.

DR. D. MURPHY: It is really the FDA's Advisory. The difference about this committee, but it is similar to your committee here, is that it is actually named in legislation and assigned certain responsibilities.

Some of the main responsibilities that it is assigned--well, first of all, I should step back and say that our office is mandated to do almost everything including regulate the practice of medicine, which of course the FDA doesn't do by the law. So we have to take all this as a little bit of a perspective of what do we really do in FDA and what was real intent. And we think the intent was

to promote the well-being of children by having those standards developed for children that we require for adults, because we all know that that hasn't happened.

There is a scientific mandate, there is an ethical mandate, and there is a safety mandate just to put them in three broad categories. We have an advisory committee that is specifically focused on a number of safety issues, to review the adverse events that are reported, has also worked to address some of the ethical issues, and there is a Pediatric Ethics Subcommittee that reports to that committee.

Dr. Nelson, who is here and will be providing a special session on Friday for the Center for Drugs reviewers on some of the implications of ethical issues in international studies. That subcommittee and that committee have dealt with a number of those issues.

They also have dealt with a number of scientific questions, such as should we keep asking for these kind of studies, because again there is an incentive involved here and there is always a push sometimes to keep asking for studies and when do we think we have enough options, when do we think we have other questions, how do you weigh that.

Our division directors often are in a situation where they would like to--and are in the process of reassessing what they have asked for and how to better construct future trials.

You can imagine that there are differences of opinion as to how strong some of the data is and how you should move forward. That committee is also tasked with doing that. We often do it in combination with other technical committees, be it a neural product or, you know, a cardiac product, et cetera.

Does that get to your question or not?

DR. LINK: I was trying to get to the idea of how you decide, you know, these written requests. So where in the organization do the written requests for pediatric studies emanate from? Does it come from that committee?

DR. D. MURPHY: No, no.

DR. LINK: So who decides?

DR. D. MURPHY: It's the committee that--well, first of all, the process is that industry is always invited to provide a proposal, and they do a lot of that. I would say many of the written requests, the majority of the written requests start as an industry proposal.

Then, the Division for which oversight is maintained for the products, then, interacts with the sponsor, because we get proposals that range from really outstanding proposals to you have got to be kidding us.

They maybe get back an inadequate letter that says start all over again, or they will get back a letter that says we think you need to try this, this and this.

In that process stage, in the past--and, as Lisa has said, things are sort of changing now, too--but, in the past, the Divisions were encouraged to come to what was called the Pediatric Implementation Team. They were not required in the past. They were encouraged, so they all did not--most did, many did, but not everyone.

But in that process, somewhere the Division would say we need to go to the Pediatric Implementation Committee and get some input. Now, that process has been codified, if you will, that they will come to that committee.

We are very encouraged, the Pediatric group is very encouraged that we have this internal committee because you can imagine the different processes that these laws have in place, that they were implemented differently, you know, you heard the history.

They started differently, they are implemented differently, they have different triggering points. And this committee, this internal Pediatric Review Committee, is charged with trying to make sure that all the--you know, that the people who may not be as familiar with all the pediatric initiatives that the pediatricians are are aware of those initiatives, how best to use them, how to make them complement each other, because there is confusion sometimes about what you can require, what you can ask for, and also encouraging them to sometimes to expand the horizon because they may be thinking they can only ask for a little bit when there is actually more that they could and should be asking for.

So, this committee, that is now its responsibility and, as Lisa said, it is not only doing it for drugs. It is also biologics.

Does that answer the question?

DR. LINK: Yes.

DR. BLANEY: How would the FDA handle it if you get four written requests at relatively the same time for an inhibitor enzyme X that is a critical pathway or critical target, and they all have an oral formulation and a

relatively equivalent safety profile?

Would you approve each of those and let the Oncology Committee figure out which trial they can do? I mean, how does that work internally?

DR. MATHIS: I think because this is such a huge area of need, we would consider issuing written requests for all of those. We would look at their individual merits and again remember that oncology products have Phase 1 studies. They have a lot of tolerability issues, so we would probably consider each of those and, if they had merit, we would consider issuing a written request. Then, depending on what happened as a result of the studies of those, they would be approved or not approved.

The office director actually signs off on the written requests so again there would have to be a lot of looking at those individual products to see how much they could benefit the pediatric population. But with such a large area of need, I can't imagine that we wouldn't want to see more products developed.

DR. WEISS: We will hear a little bit from, I think, Malcolm in the early afternoon about it. But, of course, you all know that pediatric oncology is unique as

well in terms of the Cooperative Group and issues related to, you know, small numbers of patients and how best to try to figure out what is the most important, if you could only do one trial with one class of drug, how would you do that.

I mean, that is sort of part of the complexities that factor in, in terms of pediatric oncology development. I think we will hear a little bit more about how that is actually done a little later on.

DR. SANTANA: Dianne, can you clarify for us the Pediatric Implementation Committee, and then this Pediatric Research Committee internally--are they the same?

DR. D. MURPHY: One merged into the other. The old Pediatric Implementation Team, the one which existed to look at actually Mac helped in establishing that because of the need to have some consistency. At the time we didn't have that many pediatricians. We are getting more.

It was an effort to make sure that they had that kind of input. So that was the old team, internal committee, that is now merged into this bigger committee with the various representations and, if you will, some authority now to it.

DR. MATHIS: Victor, I would add to that, that the

committee now, while previously they only looked at activities under BPCA or the written requests, we now look at written requests, we look at waivers, deferrals, plans and assessments under PREA, as well.

Because PREA is included, now CBER, or the Center for Biologic, Evaluation and Research, also sits on that internal review committee.

DR. LINK: Thank you very much. That was great.

We had a couple of people come late. Malcolm, if you want to introduce yourself, and Ken.

DR. SMITH: Malcolm Smith from the Cancer Therapy Evaluation Program at the National Cancer Institute.

DR. COHEN: I am Ken Cohen. I am from Johns Hopkins.

DR. LINK: We will now move on. Murray Lumpkin.

Introduction to International Cooperation

DR. LUMPKIN: Welcome to all of you and let me add my welcome to everyone in the room and everyone around the table. I would like to start first by thanking Jerry for his very kind and thoughtful remarks this morning.

It really has been a great honor and a great privilege for many of us in this room, and I think people

throughout the pediatric community over the past 10 years to have had the opportunity to work as a larger community to kind of take the dream everybody had 10 years ago and see how it has evolved into the reality that exists today.

We know it is a reality that we are all very proud of. But it is a reality that is only partially there to its goal, and it is one that I know all of us are going to continue to work on.

One of the things as we have gone through this 10 years that has been very satisfying in the end of the process it has been a bit gut wrenching as Elaine knows during the process, has been the fact that our Congress has now three times the original and the two reauthorizations validated this process as something of value to the larger community in this country.

I think what you are going to be hearing about today is what I consider an equally wonderful validation of what we have been doing and that is the fact that our international colleagues in the European Union have taken our particular approach and, of course, have adapted it and have, in many ways I think you will see by the end of the day, improved it to make a program that will work within

their jurisdiction and that will work to try to meet the needs of their community in Europe.

Again, I think that is a very, very nice, and a very, very critical validation throughout the international pediatric community that this is not only an approach that seems to be working here in the United States but it is an approach that our European colleagues have decided to take on themselves.

I would like to also thank Rick and Karen for inviting me to be here and all of you for coming and being part of this advisory committee. In my 19 years here at the agency, I have always enjoyed participating in advisory committees and feel that the advisory committees have always been a very, very special and unique part of the way that we try to meet our statutory mission here at the U.S. FDA.

Since we are kind of doing an international theme today, as I travel around the world with my present portfolio, one of the things I often hear people say is how envious they are of our system that we have public advisory committees and that we have the ability within our system to tap into these various wells of knowledge that exist throughout our country to try to get more counsel and get

more information to help us do our particular work.

One of the things that has been changing in the last five or 10 years is not only the way that we approach pediatrics but also the way that we approach how we try to meet our mission. Our mission has not changed.

If you look at it from the early part of the 20th century to its codification in 1977 in our Act, Congress has mandated that we do certain things to promote and to protect the health of the United States. So that mission to promote and to protect has not changed. But I think what has changed dramatically, and what is continuing to change dramatically, is the world in which we are called to try to implement that particular mission.

[Slide.]

So, what I want to talk with you about today is the reality of the international component of what FDA does. Any of you who pick up a newspaper, and have picked up a newspaper in the last day, in the last week, in the last month and the last year, realize that the international implications of the mission that FDA has is now something that is quite on the radar screen both politically and in other ways in this town and throughout this country and

throughout this world.

Whether it's pet food and melamine, such as we had last summer, whether it's heparin contamination that we are dealing with now, no matter what, basically, everything that we are doing at this point in time has an international component that is only growing.

The reality of this is--and what I am going to try to do in the next several minutes is give you a larger context in which to put the more detailed, more focused discussion that you are going to have.

You are going to be talking about the ability under various kinds of international agreements and international laws to try to work more cooperatively on pediatric oncology trials. That is what you are going to be spending the rest of the day talking about. But my task is to try to put that in, as I say, the larger international context and what is happening in how FDA is trying to meet its mission.

[Slide.]

As you look at what has happened, the reality today is that doing our business is not something that we can accomplish by only looking at things within our own

borders. Our international regulatory cooperation is no longer discretionary, and the work we do internationally and with our international colleagues is an integral and pivotal part of the work that we and our counterpart agencies perform every day.

In reality, only by going beyond our borders and looking at how we accomplish our mission, not only within our borders but beyond our borders, are we going to be able to accomplish the domestic mission that Congress and the American people have given us.

[Slide.]

The 21st century reality is that the world we live in and the world in which we as FDA have to operate, has indeed radically changed and it continues to do so. The products that we are called upon to oversee, whether they be human drugs, animal drugs, medical devices, human biologics, or 80 percent of the United States food supply, these are all global commodities.

No longer do we live in a world where food is grown in your back yard or within your state, as it was in 1906 when the Act was first promulgated. No longer do we live in a world where most drugs are made in North America

or Western Europe. We live in a world where these are globalized commodities, not only where they are manufactured but what we are finding now, where they are discovered, where they are developed.

By that I mean where the clinical trials are being done, where they are manufactured, how they are manufactured, how they are authorized, where they are authorized, how they are promoted, how they are marketed, and how they are used by consumers, practitioners, and patients, are all global issues at this point in time. They really are no longer local domestic either from a European perspective or from a U.S. perspective.

[Slide.]

One of the things that we like to point out is that our borders now are indeed still geographic boundaries. But they are not barriers as they have been in the past. We have known for a long time they are not barriers to disease.

That is even becoming more evident as all of you know as well as I. They are no longer barriers to information flow and obviously in the world of the Internet and nanosecond communications, that is a truism that is only

becoming more and more apparent.

They are no longer barriers to product acquisition as we find every day when we see hundreds and hundreds, if not thousands, of packages of drugs coming into the United States or trying to come into the United States as people order these from various and sundry Internet pharmacies around the world. But they are barriers to our jurisdiction and they are barriers to the jurisdiction of our counterpart agencies around the world.

[Slide.]

When we look at what has happened in the United States, when we are looking at the amount of food that is now imported into the United States, when we look at where our active pharmaceutical ingredients come from, when we look at where our finished dosage forms are coming from, no longer, as I said, are these issues that are domestic.

Depending on the food commodity, here in the United States we import between 15 and 20 percent of our total food supply. When you are talking about seafood and other products that we are responsible for here at the FDA, we are now upwards to 80 to 85 percent.

Most of the active pharmaceutical ingredients that

are used throughout the world now are no longer made in Western Europe and North America. They are predominantly made in China and India. And we are seeing more and more the reality in product manufacture being something that you cannot assign to any one region or country.

The reality is that these products are assembled and you have components that come from all parts of the world that are brought one place and assembled, or assembled in several places and then transported and distributed around the world including the United States.

[Slide.]

Given this new reality of trying to regulate global commodities in a globalized world that we have today, none of us, whether it is the EMEA, whether it is the U.S. FDA, any of us who have these regulatory responsibilities, none of us have the financial, the human, or the scientific resources to do all that our parliaments and our people ask and expect of us.

As I said, when we work together and we talk about our challenges, we all realize that we cannot meet our individual missions by only looking within our borders.

[Slide.]

As many of you might be aware, when we went through the summer last year of the melamine situation with pet food, with the toys that had lead on it, with the tires that were exploding on the expressways, there was an outcry in the American public that was reflected on the Hill and throughout our present government, that indeed something needed to be done to look at this in a more systematic way than had been done in the past.

President Bush, under an executive order last summer, put together an Import Safety Working Group that was headed by Secretary Leavitt and involved 10 to 11 different cabinet level officers which came up with a now public Import Safety Working Group Action Plan of which our Food Protection Plan--and the work that we are doing on the borders.

As we look at how we try to help assure the safety of all of the products for which FDA is responsible in the United States, one of the things that has come out of this is the reality that now we can no longer have a model where we try to inspect bad products out at the border.

The idea that it doesn't matter what happens outside the United States when these products hit our

borders, we will have sufficient resources and ability to inspect out bad products is simply not reality and is not going to happen in the near future.

The model that is now being proposed, the model that we are now all working towards, is a model where indeed the borders become a place, not of inspecting out bad products but where we audit in products that we are assured indeed have the quality has been built in at the point of manufacture. This requires us to, as Dr. von Eschenbach says, go beyond our borders.

[Slide.]

Other things in the 21st century reality is that no national or regional regulatory authority has a monopoly on good science or good regulatory practices. I think you will see that as you meet on yesterday and a lot of our colleagues from the EMEA, there is a tremendous amount of good science and good regulatory practice that comes out of many of our trusted regulatory counterparts around the world.

As we as regulators around the world work together, I think we are convinced that the sum of our parts is clearly superior to their individual value.

[Slide.]

Regulatory cooperation is no longer discretionary. We believe it has to become a standard operating procedure of any 21st century flagship medicinal product regulatory authority of which we here at the U.S. FDA obviously intend to continue being one--that is, a flagship medicinal product regulatory authority.

[Slide.]

The reality is that, blessedly, we are not all clones of each other yet and that as you travel around the world, as you travel around our own country, there is tremendous diversity in. And I think it brings great richness to, the legal, the societal, the medical practice foundations upon which each regulatory authority must act within its own jurisdiction.

[Slide.]

Now, in 1997, when Congress put into law what it thought FDA's statutory mission was, this is the first part of that. It says, "The Administration shall" and it lists (1) and (2)--and these are the things that we have always thought about, that we are to promote the public health by doing certain things and, with respect to these products, we

are to protect the public health by doing things, such as the area that you guys are interested, that human and veterinary drugs are safe and effective.

[Slide.]

But Congress also put a number (3). And this is not corollary to number (1) and (2). This is equivalent to number (1) and (2). It simply has to be number (3).

Congress said part of our statutory mission was to participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.

I think as you talk with our European counterparts today, when you see how Dianne and our pediatric cluster with the European Union operate, indeed, this is an integral part of our mission and how we do our work in the 21st century as we think it needs to be done clearly but, even more importantly, in fulfillment of the statutory mission that Congress gave us.

[Slide.]

We have a lot of international cooperative activities that are going on at this point in time. I am

going to give you primarily a look at our work with the European Union because that is the group with whom you are going to be working most of the day.

But what we are trying to do with these is through our bilateral and multilateral efforts, figure out how we can leverage best the human, the scientific and the financial resources that we have here and that our counterpart agencies have around the world so that we can use their experience, we can use their resources--and I am talking here about our key trusted regulatory authorities around the world--to try to avoid duplication of effort, in the case we are talking about today, to try to make sure that children are not becoming commodities because of incentive programs that are now in various parts of the world, to make sure that our activities are efficient, and to allow us to focus the resources that we do have on higher risk areas of concern.

If we can't do everything, then, we need to at least be able very realistically to explain how we decide which things are most high risk and where we are using the resources that we have.

[Slide.]

What we try to do and particularly as you will see in our interactions with the European Union, is find ways that we can focus on specific information exchanges, on timing of those exchange and, most importantly, institutionalizing the process.

Obviously, as those of you who are involved in international work know that personal relationships are extremely important but also the institutional relationships are important.

As you will see today, there is no deeper personal and professional relationship than Dianne and Agnes have developed over the years that they have been working together. But what we want to make sure happens is that if, God forbid, sometime the day will come that Dianne says she is tired of working here, or Agnes says she is tired of working at the EMEA, that this program would not fall apart because it rests on personal relationships but that it would continue and build on what they have built because it has been institutionalized.

One of the things I wanted to mention in this previous one, one of the things that is actually most exciting and most helpful I think many of us have found in

working with our colleagues such as Agnes and others at the EMEA, is that within our own country, nobody else does the job that we do.

We are the only people in the United States that have this exact job to do. And when you are looking for a peer to talk with about a certain issue, when you want to just bounce something off of somebody, when you want to do a reality check on an issue that you are struggling with, there really is no one in the United States that you can call outside of the FDA to do that kind of informal peer sounding board kind of situation that we all know is very, very important.

But we have peers sitting here who are from London, and we do use them and they use us. And we have peers in Canada. And we have peers in Australia, New Zealand and other parts of the world that you will see in a few minutes where we can, by calling them up and using a lot of the ways, the formal frameworks that we have developed, use them as informal and formal peer sounding boards.

[Slide.]

The way we try to do this is through what we called "The Pyramid," which is primarily a framework that

allows us to interact with our counterparts around the world in ways that you will see very specific to your work today, and it is based primarily on a foundation of a confidentiality arrangement and then, based on that confidentiality arrangement, working out together the kinds of issues, the kinds of information exchange, the kinds of initiatives that we are going to focus on each year.

[Slide.]

These are the countries with whom we have confidentiality arrangements at this point in time. We have a special provision within our regulations that allow us to go into confidentiality arrangements with foreign counterpart agencies if those agencies are able to demonstrate to us, then obviously, we have to demonstrate to them, that they are able to maintain confidential the information we send to them at the same level that we are able to do here it here in the United States.

So, this doesn't open it up to everybody in the world by any means. It opens it up to certain regulatory authorities that have the legal framework and the actual ability to maintain confidentiality of information that we are required to maintain confidential here.

You see the people, the various countries that we have been able to do this with, one of them being the European Union and the European Medicines Agency or EMEA.

[Slide.]

What these confidentiality arrangements provide to us is a legal framework. They don't require us to do anything but they provide us a legal framework to share with our counterpart agencies certain otherwise non-public information, such as commercial confidential information, pre-decisional information, investigative information, compliance information.

What we are not allowed to share under U.S. law, even with the confidentiality agreement, is trade secret information but, for us, that generally is a very limited subset of the information we have here.

It primarily has to do with certain parts of the manufacturing procedures that go on and it has not been a tremendous barrier in most situations to the kinds of discussions that we want to have with our counterpart agencies.

What this allows us to do is to share this information and it not become public. If we didn't have the

confidentiality arrangements, and we were to give this information to a counterpart agency, under our law, that agency is no different than anybody else in the public. And, having given it to them, if somebody else were to ask for it under the Freedom of Information Act, we would obviously be obliged to give it to anyone else in the public.

By having the confidentiality arrangement, that provision does not kick in and we are allowed to share between counterpart agencies under the auspices of this legal framework.

[Slide.]

What we have tried to do then is once we have put these confidentiality arrangements in, is to work with our counterpart agencies to figure out what are we actually going to do using this tool to try to leverage the resources and try to really have a situation where the sum of our activities is more than their individual components.

That depends really on the level of capability of our counterpart agency, the history of our interactions, and the level of confidence we have in what they do and how they do it. Clearly, none is more robust, none is more active

than our interaction with the European Union and the EMEA on medicinal products.

[Slide.]

As I was saying, the European Commission and the European Medicines Agency are two of our most important counterpart agencies and the ones with whom I think we all feel we have one of the most developed, the most bilaterally productive relationships--personally, professionally and organizationally.

[Slide.]

The implementation plan and the confidentiality arrangement that we have with the European Union are public documents. They are on our website, as are the implementation plans and the confidentiality arrangements we have with other regulatory authorities around the world.

With the European Union actually, in reality, as you will hear as we focus down on the pediatric piece, we at this point in time basically have almost daily interactions with our European counterparts on the various products that we share. Our plans have helped us focus our work on that .

[Slide.]

Formally, we meet with our European colleagues at

least once a year at which time we, at the senior executive level, agree on what the initiatives are and what we are going to be focusing on for the next year. But the reality is the great majority of the work is done informally, innumerable, basically, on a daily basis each year, or each day, either in telephone, or in cyberspace, or by having the great pleasure of having our colleagues come here and participate in the work we do here, or having our colleagues go and participate in their committees, to do secondments at the EMEA, which a few years ago I had the great pleasure of working at the EMEA for three months.

We have had people from EMEA come and work with us here for various periods of time.

[Slide.]

One of the things, as this relationship has grown, is that this is not a relationship only at the senior executive level. This is a relationship now that has begun to permeate down through both organizations and, in certain areas, of which pediatrics is one, at the technical working level within both organizations, we have created what we call clusters.

The pediatric cluster is headed by Dianne and

Agnes. We also have clusters within the world of vaccines, pharmacogenomics, oncology, orphans and product safety.

Rick heads the cluster on the oncology side. These clusters are really groups that are bilateral working groups that meet monthly, if not more often, on the telephone or if they happen to be in the same place at the same time, to talk about specific issues and each other's products that they are working on and gives them a real opportunity to leverage each other's scientific perspectives and insights and regulatory resources.

[Slide.]

I am not going to go through this because of time. This just gives you a history of our working with the European Union and the European Medicines Agency over the past five, six, seven years.

[Slide.]

We do several things when we work with the European Commission and the EMEA. There is a great deal of what we call upstream regulatory cooperation. This is where we are able to share advance drafts of legislation from the EU. They share those with us, we share advanced drafts of regulations with them. We get their input before these go

public for public input.

We look at implementing technical texts, such as guidelines. As I mentioned, the staff exchanges, and the bilateral meetings and workshops, and the kinds of things that are going to happen here today.

[Slide.]

On a regular basis, on a quarterly basis, we exchange with each other the list of the newly submitted--I am using the European abbreviation here--the Marketing Authorization Applications known as BLA and NDAs here, so all the new NDAs that have been submitted or all the Marketing Authorization Applications that have been submitted there, we know what is in each other's shop, we know what is still undergoing review. We know what the marketing decisions are that have been made and whether there are any post-authorization applications that are coming in.

So, we, on a routine basis, keep each other informed of the workload that they have, what things are in each other's shop, so that our people, as they are reviewing these, as questions come up, they are able to utilize the expertise and the sounding board that our colleagues provide

for us.

[Slide.]

We also try to figure out the best way possible to leverage each other's resources when it comes to doing GCP inspections, GMP inspections, sharing the results of those inspections with each other and, hopefully, as time goes on, getting better and better, using that kind of information to plan and to do risk-based decisionmaking on where we need to spend our inspectional resources and where we can rely on the information from others.

[Slide.]

Clearly, we have ad-hoc exchanges particularly when there is emergency information, when there are issues that are pertinent in an emergency way to public health, or when there are going to be major news events in either here or in the European Union.

We give each other as much of a heads up on that as we possibly can so that each of us will understand what is happening in the other jurisdiction and be able to respond to queries from the press and from our political leadership in our various jurisdictions on what is happening on the other side of the Atlantic.

[Slide.]

We have various ad-hoc exchanges. We have a system of what we call Parallel Scientific Advice, which is a pilot program that allows companies to get various developmental advice from the European Union and from us in parallel, to try to harmonize as best as possible the approaches to drug development that are happening on both sides of the Atlantic.

This is something you will hear more about as the day goes on, on how we are trying to work to develop a pediatric parallel scientific advice, as it were, to try to deal with development issues in, as was pointed out earlier today, smaller populations where we don't have a lot of wiggle room, as it were, when it comes to trying to design programs to give us the information we need in our pediatric community here and the pediatric community in Europe needs to do their business well.

[Slide.]

You have got all of these in your background documentation here.

[Slide.]

I just want to end with this slide. One of the

things that you are hearing a great deal about now in the paper is something that Dr. von Eschenbach has been talking about, that Secretary Leavitt has been talking about and people on the Hill, as part of our Beyond our Borders initiative, is the reality that again we cannot do our job well by simply having the FDA sit within our own borders.

If we are going to make our borders, as I said at the beginning, a place where we audit in good products as opposed to try to inspect out bad products, we need to have better information, we need to work with our counterpart agencies better.

We need to work with industries overseas that want to export their products to the United States to make sure they understand what the expectations are here when it comes to quality and safety and that they understand what needs to happen if their products are going to be audited in as good products at the border.

In order to do this we believe that we can most effectively do this by establishing FDA offices outside the United States. This is not rocket science. Many other parts of our government have done this. This is not something historically the FDA has done.

We are in the process right now of establishing an FDA office at the U.S. embassy in Beijing. We have had discussions with the Indian Government, with the Jordanian Government in the Middle East.

The five areas that you see there, China, India, Europe, the Middle East, Latin America, are the first five geographic areas that we are looking to establish FDA offices overseas. And these are not offices just to do inspections.

Clearly, to be able to do inspections more timely is one part of the office mission. But another part, as I said, is working much more closely on a day-in, day-out, full-time basis with our counterpart agencies, with the industries in those areas who wish to export to the United States, to make sure that indeed the products that come in, whether they be pediatric oncology drugs, whether they be the food we eat, whether they be the medical devices and biologics, or adult drugs or animal drugs that are coming in, that indeed they are products that Americans can be confident in, that they meet the standards that they expect and the standards that we expect these companies to meet when they send their products here.

So you can see the international component of what we do is an incredibly growing important part of what we do here and, as you will now begin to focus on, the piece of this that involves the development of pediatric drugs, and particularly development of pediatric oncology drugs, is one piece of this overarching internationalization and globalization of all of the aspects of what we do here from product development, discovery development, authorization, marketing and use by patients and consumers.

[Slide.]

I again thank you for coming. I hope this has helped put it a little bit in perspective of where we are going at this agency, where we are at this agency when it comes to globalization and internationalization.

I wish you a great day today. Unfortunately, I am going to have to leave because the Commissioner has been asked to do a hearing next week on, surprise, surprise, foreign inspections, and I have to go help prepare him, which started about 30 minutes ago.

If you have any quick questions for me, I am happy to answer them. Otherwise, I will leave you in Rick and Karen's and Michael's good hands here today.

Clarification Questions from Committee

DR. FINKLESTEIN: I have a small technical question. Does the term AU supersede the fact that you did not list Spain and Italy in terms of the confidentiality agreements?

DR. LUMPKIN: That has been a very interesting part. When I listed them up there, our confidentiality agreement with the European Union is with the Commission and with our colleagues at the European Medicines Agency.

When there are people from the member states who are functioning in the capacity of working with or for the EMEA, they are covered no matter which of the 27, 28 member states that they come from.

However, as you probably know, with drugs in Europe, you still have the situation where many drugs are regulated by the national member states. They are not centrally authorized. This, for example, came up with the flu vaccine issue in the United Kingdom several years ago. That is not a centrally authorized product, that is a nationally authorized product in the United Kingdom.

It is not under the jurisdiction of the European Commission or the EMEA and, in order to work on that

particular product, we needed a specific confidentiality agreement with the United Kingdom.

The ones you see listed that happen to be member states of the European Union, those are actually individual bilateral confidentiality arrangements with the national authority in that particular country.

So, it is with the MHRA in the United Kingdom, it is with ASAPS within France, it is within BPharm within Germany. We do not have specific ones with all 27 member states at this point in time.

There are some that simply--there is not a great deal of trade in any of our products between those countries. So it really hasn't been worth our effort to try to go through the process of doing a confidentiality agreement.

We tried to look at the countries within the European Union that we have nationally authorized products that we need to work with them on, and that is how that list came up there.

DR. BLANEY: Do you foresee a day when it would be possible to have a simultaneous review by the FDA and the EMEA without delaying access?

DR. LUMPKIN: You know, part of the issue is--and it is something that we do look at--part of the issue is when the companies submit them, are they even submitting them simultaneously. I mean, you can't do a simultaneous review if you don't have them.

Also, are they submitting the same thing, do they want the same claims in both jurisdictions, are they submitting, you know, the same packages.

What we do see happening already is the issue of when they are--even if they are not submitted at the same time, if they are being done sequentially and there is overlap, there is discussion back and forth so there is review and discussion of what is happening along those lines.

In reality, I think when you look at the time frames that the EU has for doing their reviews, and the time frames we have for doing our reviews, they are essentially the same.

DR. BLANEY: I guess that was a single unified review so that there wouldn't be an application to two different agencies.

DR. LUMPKIN: Well, at the end of the day, I think

there would always be the application to the two agencies, because neither of us have authority to make a decision in the other jurisdiction.

There is a great deal we can share on the science, there is a great deal we can share on the process and the design. But there is a lot that is not harmonized. I mean, the laws are not harmonized. The medical practices are not harmonized. And, you know, at the end of the day, one of the things, as we were talking about not being clones of each other, the risk tolerance within the various communities is not the same.

So, you will sometimes find that even given exactly the same data set, we come to different conclusions. The committees in this country will come to one conclusion and the committee in Europe will come to another conclusion for various reasons.

I have often had companies have said, you know, to me, well, wouldn't it be great if we just had one review, or if somebody said yes, you would just take their yes, if the European Union said yes, you would just take their yes.

I said yes, that's fine, but that means when they say no, we take their no. I mean, if they are competent to

say yes, they are competent to say no, and is that really what you want if, indeed, within the communities, the risk tolerance might be different even looking at the same data set.

So, I think the idea of having one review, one decision worldwide, has its up sides when you kind of hear it at a theoretical level. But it really has some down sides, too, and that what we have now is the ability to share, to talk, to use each other's science, to use each other's experience, but yet then to come back to within our own jurisdictions and our own communities and say, okay, here are the data--you know, here are the benefits, here are the risks. Are you willing to accept them within medical practice, within the realities of what happened within our own jurisdiction?

DR. REYNOLDS: Do you have any similar relationships with Japan as you have listed for the other countries?

DR. LUMPKIN: We do. We have confidentiality agreements with the Ministry of Health, Labor and Welfare, and with the PMDA there, which is the organization that does human drugs and human devices.

We do not have as robust a relationship when you start talking about the details and the kinds of things that you will be seeing here, as we have with the European Union. Ours with the EU is the most, it's the oldest, as you can see, it's the most developed.

We are continuing to develop our relationship with Japan. I think the European Union, you all just signed recently a confidentiality agreement with Japan, right? About a year ago, yes. So, it's triangulating that way.

We have for many years had a relationship with them through the ICH process, the International Conference on Harmonization. I think probably it is through that mechanism that we have the most interaction with Japan.

The other part, though, with Japan, I will say that has been extremely active, is in the world of devices and under the Global Harmonization Task Force, the Japanese have been very active with us on the device side of the house.

There is a special program called the Mansfield Fellows Program, which is a program for U.S. Government employees, that allows U.S. Government employees to go to Japan and to work in their counterpart agency for a year.

But your agency has to support them for two years because you have to go to the State Department and do intensive Japanese language training for a year and then go to Japan for a year.

We have been the agency that has sent the most people to Japan under that program. We have had eight people from the FDA over the past 10 years go to that program.

Everybody from medical reviewers to chemists, to inspectors, to project managers, the entire gamut of the disciplines that we have here go and work and really begin to see the inner workings of how the Japanese regulatory system works.

I think that, for us, has been the most helpful to actually begin to understand it by having our people go and work there for a year. Then they come back here and they become the way to connect the dots with the people with whom they have really established very good personal and professional relationships.

DR. D. MURPHY: I just wanted to add to that from a pediatric perspective, we have had some of our Japanese colleagues here to present to us what they are doing and how

they are trying to develop their pediatric programs and tend to now include them.

They participate quite a bit internationally when we have pediatric programs. So those relationships are being built, and I think are going to continue to grow.

DR. LUMPKIN: It reminded me when Dianne was talking--I mean, one of the biggest areas where we have had a very intense interaction with our Japanese colleagues is on the safety profile of Tamiflu where we had a lot of the issues and the concerns coming out of Japan and out of the safety reports in Japan.

Actually, the people came and participated in the advisory committee here when we were talking about the safety profile of Tamiflu and it was their participation and their explanation of why they thought this was happening in Japan, and trying to put the clinical safety profile and the reports they were seeing in a Japanese context, that was really quite helpful.

DR. LINK: I just have a follow-up question of Dr. Blaney. It would seem that when you talked about the different agencies entrusting one another in terms of making decisions, it is really the interpretation of the data

rather than the actual delving into the data. So I am still wondering why there isn't an efficiency.

In other words, you take the analysis that is done, for example, by the EMEA, you may interpret it differently, you may say that this risk-benefit ratio is not appropriate for us or we would interpret it differently and may or may not go ahead with licensing on that basis.

But the question is whether you have to troll through the database and get the same toxicity data over and over again, or can't you simply take their report and say, here are the toxicities, you know, and take their executive summary, if you will.

It is sort of like a central IRB. You know, an individual IRB may not agree with it and may still turn it down, but I mean the science is the science, here is the data. Why is that so difficult for you, why do you have to go through and troll through it yourself?

DR. LUMPKIN: A couple of answers. Number one, I would say even the Europeans don't do it one time. Actually, one of the interesting things about their system is they have two people do it.

They have, not people within the EMEA that are

actually reviewing it like we have in divisions but they use the national authorities within their member states as their reviewing capacity, and they always send it to two. They have two independent looks at the data and then bring it together.

I think, you know, the idea of the quality control that you get, and the idea of having more than one person delve into the data, validate the data, look at what is there, see where the red flags are, see what the questions are that come up, adds to the richness and adds to the value of what is going on.

I think also as we said earlier, we look at the data in this country for the most part from the bottom up, looking at validating the data, looking at the analyses, looking at what happened. Then, once you do that, having the robust discussion, looking at others who have looked at the data, not just looked at the summary but have looked at the data, had the experience of doing that, and comparing are they coming out at the same place is of value.

DR. LINK: I am going to challenge you then, because now you know that they have already reviewed it twice. So you are saying that you don't even trust two

reviews, that you have to do it yourself.

So, the question is, is there some way in terms of harmonizing, maybe reviewing it together? One of the frustrations is that it is not so much that you come to different conclusions, it's that you take so long to sort of go through a data set which is the same data set ultimately.

DR. LUMPKIN: I guess I would argue with the idea, you say it takes so long. If we were here 15 years ago, 20 years ago, I would say you would have a point. I think at this point, we would argue that the review process itself is not the rate limiting factor on access to drugs at this point in time. It has been made as efficient as it's going to be made here in this country and in the European Union through the processes that are in place.

I mean, the rate limiting factor is the development.

DR. LINK: Time was a bad word--personnel, budget is maybe the limiting factor here, which will be. I mean, we hear all the time you don't have enough people around to do what you have to do. So, this would be a way of sort of leveraging on the fact that other people with, as you admit, the same competencies and your partners are doing it, it

would seem to me that there would be benefit of relying on them.

DR. LUMPKIN: I think we are in the confidence-building stage. I mean, as we have talked about, we do a great deal of sharing of the information, of sharing opinions, of talking as we go through the reviews, which is extremely helpful on that.

But it is still an issue I think at the end of the day of putting it in the context of your own clinical community, of your own jurisdiction, or your own medical practice and trying to figure out, you know, how does this fit, are there questions that are coming up and how does it fit within the context of what the company is asking for as far as marketing profile within that jurisdiction, which is often not exactly the same because of the medical practice issues.

DR. LINK: Yes.

DR. BLANEY: I just wanted to say at the end of the day, the review process may not be our rate-limiting step. But in pediatrics we have a unique challenge that these drugs do become commercially available so we have a narrow window of opportunity before people start using them

off label in the pediatric oncology population.

So, if there was a way to do even, you know, to streamline the process because, if we are going to try to develop international collaboration and do a trial that has input from both sides, we can't start that process until we know what is going to be accepted by the agency.

DR. LUMPKIN: I think you will see when you hear the discussion, that is exactly where it is going. That is exactly what part of it is.

DR. D. MURPHY: I would like to just re-emphasize what Mac has said because I know you are thinking of oncology. But I would ask you to think outside of oncology, too, because there are many other products, is that when you get into the data, even in English in our own agency with different people looking at the same words that are high level terms and what is behind that and whether that should trigger looking into lower level terms and where you go.

I mean, language is important and behaviors, because sometimes somebody will read a case report and it may or may not, it is going to be dependent upon what your knowledge is, too, as to what some of these things that are happening, certainly from some of safety perspectives.

So, I think there is a definite difference in how people--what they bring to the table and when they are looking into the data itself that does enrich and does inform from their medical practices and their use of terms to describe things. So, I do think that there is always going to be that part of it, too, that we have to deal with.

I mean, I just refer you back to the SSRIs and tell you that that was, you know, a pediatrician looking at medical terms and saying I want to look at different medical terms. And that is how that evolved.

DR. LUMPKIN: I think very much as you will hear today, as we work more and more together to have agreement on the clinical trial design, it will push the review being a very similar review, if not the same review all the way through.

I mean, what has been problematic in the past is that the clinical trial designs have not been the same or the comparators have not been the same. Whether one agrees or doesn't agree with the surrogate has not been the same, which obviously leads to different applications, different asks and different reviews.

My bias is, as you will see here today, I think on

the pediatric side particularly and Ped Onc, if we can get to the point where there is agreement on both sides as to what the development plan is going to be, it will simply push into--I mean, the review element will be the audit at the end rather than the weighing that it has been in the past.

DR. D. MURPHY: I need to correct my statement. That was a psychiatrist who practiced pediatrics, I want to make sure I don't mislead people.

DR. LUMPKIN: Thank you all again very, very much.

DR. LINK: Now we will move on to actually hearing from the Europeans describing it themselves, so we don't have to hear the American version of it from Dr. Saint-Raymond.

DR. LUMPKIN: I have to admit it is always fun when I get to hear their version of our system. It is very interesting to go, oh, is that the way it appears, you know, it's a great exercise.

DR. LINK: So many Americans are walking around Europe with Canadian backpacks.

European Medicines Directive

[Slide.]

DR. SAINT-RAYMOND: Good morning, everybody. Thank you very much. I am going to have to say first that I agree completely with what Mac said before and it's really very well describing our feeling. At least on this part we completely agree.

Thank you for inviting me and giving me the opportunity to explain a little bit what we do in Europe and especially with a special focus on oncology. I apologize for my bad voice and my poor French accent. I hope you will be able to follow.

[Slide.]

We have a new regulation in Europe. It took us a long time to get it. The first time I came here was in 2001. We were looking at the proposal, and it came into force beginning of 2007. So you can see in the meantime you have revised yours twice.

We don't intend to revise it before 10 years, at least what you learn today is probably valid for 10 years, which is more difficult for us here because it change all the time.

The objective of our legislation, what we call a regulation, is that we will increase research into medicines

for children, that we will increase the availability of authorized medicines, and that we will increase the information on these medicines and the use for children; but this should be done without unnecessary studies in children.

This is an issue as you mentioned earlier in the one question, what do we do when we have similar applications and without delaying the authorization for adults.

[Slide.]

So, there were a number of pillars in this regulation and I will try to keep it at the high level for you. But I am happy to answer any questions on the details.

The first point was creating a committee. We have committees at the agency. They are not like here, they are not public. They are made up of representatives of the member state. They are an expert committee but they are meeting every month at the agency--which is making our life difficult because we run all our procedures by cycle of month, and they only meet two or three days in London, which means that the other time we don't have them at hand to discuss the application.

There will be measures for new and patented drugs,

measures for off-patent drugs. The tool will be the pediatric investigation plan--and I am going to explain what it means--and many other measures. This is a very complex regulation.

[Slide.]

So, the committee, as I said, like all the committees in the agency, is an expert committee. So most of them are pediatricians--a few of them are oncology actually--but it is a mix of academic people, of people from regulatory agencies and so with different backgrounds and different complementary views.

The regulation or so asks us to have a number of qualifications in this committee, pharmacists, research ethicists, and so on, and we will have patient representatives, three of them, and has professionals.

They meet monthly at the EMEA for three days, which is already a lot because they travel from far and they have to spend a lot of time working in between meetings. They will take the scientific opinions, scientific decisions. The administrative decision will be taken by the agency, but really the consent is assessed by the committee.

[Slide.]

So, this committee has elected a chair, so it is also a bit different from your system. We have 5 members, which are common members from the CHMP, the committee which decides on approval of drugs for Europe.

We have 22 other representatives, so we add up to 27 because we are currently--when I left Europe at least it was 27. Maybe when I come back we will have more, but it increases all the time.

We have 3 patient/families' representatives, no children, but parents probably, and 3 health care professionals. So, these members have not yet been appointed but the committee is already working.

[Slide.]

For all new drugs which have a root in Europe--because you may know that we have two systems which run in parallel in Europe. We have the national system and the European system. But here we are talking about everything. And when I said drugs, I mean biologicals, anything. We don't have two legislations like you have, so every single medicine or product, as we call them, must have something about pediatrics.

Normally, they must submit at the time of

marketing authorization application, the result of an agreed pediatric investigation plan, development plan unless they got from the committee a deferral of the studies or a waiver of the development, but every single drug must have something.

I am not talking about generics, of course, because it's a different situation, but any new drug.

As a reward, a little bit like based on your system and, as Mac said, we have tried to take the good ideas from your system. They will get 6 months extension of the patent but under the condition that they were compliant, that they meet the requirement of the pediatric investigation plan as decided by the committee, that all results are in the product information, and that the product is approved in all 27 member states.

So, this means that the children in Europe have the same right to access of medicine. There is no country that is excluded because the market is smaller.

[Slide.]

So, the same will be true, a little bit like your system, when they come for a new indication, a new route of administration, or a new formulation, and they will have to

submit the result of an agreed PIP unless they have a deferral of the studies or a waiver.

They will get the same reward. Like your system, they will get only once. They cannot multiply the extension of the patent and they meet the same conditions.

So, we cover the new products and the on-patent products.

[Slide.]

Now, the orphan drugs are also included in this legislation. But here, because we know they affect children, it may be more difficult to do studies. This is particularly relevant for oncology because most of the pediatric oncology conditions are actually orphan conditions.

Normally, in Europe, an orphan drug, designated orphan drug receives 10 years of market exclusivity. Here, they will receive 2 additional years, so 12 years including when they are only for children.

So, there is also an incentive for orphan drugs to be authorized in Europe but they have the same obligations, of course.

[Slide.]

Now, off-patent product, we knew it was an issue, because companies have no commercial incentive to study these drugs. We knew of the issues, maybe relative lack of interest in developing these drugs, so there is a procedure in Europe, which is optional here.

Before it was mandatory. At this time it's optional, which we cover only the pediatric indication or indications, the age appropriate formulation, so they will need also to agree a development plan with the committee, and they will need to be compliant. They will need to put the results in the product information and, as a reward or as an incentive, they will get data protection for 10 years, which is what a new drug, which is probably your exclusivity, what the new drug receives in Europe.

So, the pediatric indication, the pediatric formulation will be protected against generic competition for 10 years.

[Slide.]

So, the Pediatric Investigation Plan, it is proposed by the company. The company comes to the committee submitting the data that they intend to collect. And they must come by end of Phase 1 for new product, which is very,

very early because I know you are not discussing pediatric at that time.

We also know there is a high attrition rate of products at that time, so we are very conscious that it may be additional work for companies. But, at the same time, if you want to discuss the development plan for purely pediatric products, you need to do it at that time.

If you want to integrate the pediatric development even according to the ICH guideline E-11, which says when you should start developing in children when there is a high need. Then, it may be earlier than when the drug is approved for adults.

This allows the company to modify the plan with increasing knowledge. So there is a dialogue which is set up in the regulation. But the plan, itself, will be first discussed, modified potentially by the committee, and agreed and sometimes unfortunately refused.

We have a short deadline, so that you have now extended your review time to 6 months. We have 60 days, so that is two committee meetings, because they meet only twice in 60 days. And we can extend by 60 days if we need more, additional information from the company. But that is a very

short time, and I can tell you we are struggling.

This opinion, scientific content is followed by an administrative decision, which is taken by the director of my agency. But this will be binding on the company. Binding means that if a company wants to come for Marketing Authorization in adult, if they didn't like what we said, they will be blocked.

They will not be able to submit their Marketing Authorization in adults, so there is a very strong stick to make sure that all product of interest, not just those that were of interest for companies are actually studied potentially if there is a need.

[Slide.]

So, this plan will cover everything, the quality aspect, the age appropriate formulation. It will cover the nonclinical and the clinical safety, so we can ask for juvenile data if necessary. We can ask for mechanistic studies if there is an issue with the toxicity. We will also ask, of course, for efficacy. The pediatric population for us in Europe is 0 to 17 inclusive and not to 16, but that doesn't make a difference.

Of course, if a plan has been made here, and the

written request has asked for studies in 0 to 16. We are not going to ask for a study from 16 to 17.

There is a very important point. We don't have an explicit link to the adult indication, which can be read both ways. They are not obliged to follow the adult indication. The plan can be wider than the adult indication.

At the same time, we know from previous discussion that initially, there was the intention to say that the committee could ask for anything, as many indications that they want in every domain, so it was a very different way of approaching drug development, making it mandatory for companies to develop in areas where they were not interested.

This has disappeared from the legislation, so there was clearly the intention to be maybe a little more reasonable in the way we approach development in children versus development in adults.

At the same time, there is nothing which tells us that we must restrict the pediatric investigation plan to the adult indication. So we are trying to take sort of broader look but at the same time being reasonable with

companies because we cannot ask them to develop 20 indications at the same time even if there are 20 indications of pediatric interest.

[Slide.]

In this plan after review by the committee, there will be the development timelines exactly like in the written requests and we will specify sometimes that they cannot start the study in children before they get evidence of benefit-risk, a positive benefit-risk in adults. So can be quite strong in the way we want them to get enough data before they start studying children.

We will, of course, specify what needs to be done for the formulation and its content, excipient, additive, coloring agents, and so on, and the results will serve as a basis for the approval. So they should really be not just information, they should lead to potentially a full pediatric indication.

[Slide.]

Of course, we have waivers and deferrals. They can come from the applicant. They come for prostate cancer, say, we want a waiver of the pediatric development and that is agreed. It can be for a subset of the population, for

the neonatal or, on the contrary, for the adolescent.

We have already published, also in line with what the FDA has done, a number of conditions for which like Alzheimer's, Parkinson's diseases, and so on. It is unlikely that there will be cases in children.

In some situations, there are a few cases in children, but we know it is not possible to study the drug.

The deferral I mentioned is the time of the start of the study and the time of completion of the study. Some company wanted to understand it as a deferral of the submission of the plan. I said no, no, no, you have to come early. We will say that you don't start the studies now, you wait, but you need to come to us early.

[Slide.]

So, just a summary in terms of for a new product. If we consider this sort of standard approach, which of course is very simplistic and is not always the case, the first submission in yellow is the first submission of the plan, end of Phase 1. Then we expect that there will be modification of the plan and, before the submission of application, we will check that there is compliance with the plan as agreed. Then we can go through the regulatory

process if approval, post approval.

If there is a waiver, we expect the PIP to be submitted at the same time. But the studies will be done only, for example, after positive benefit-risk in adults.

[Slide.]

So, to try to keep it simple, each plan corresponds to an active substance or a combination of active substance from one company.

But, of course, because a product may not be only studied in one area, they may come and cover more than one indication and, so far, we have seen, in general, about two indications per product.

[Slide.]

So, we have seen so far, the committee was established in July and started working in August. So, so far, we have seen already 180 applications, more or less, which is quite a lot.

This represented more than 300 indications or conditions and, among these products, this application, about a third were for already authorized products, so two-thirds for non-authorized products which were starting.

[Slide.]

In terms of the therapeutic areas of the pediatric plans, we have seen that oncology was about 14 percent. Other areas were covered as well, and we focused on the work that Herold underlined today. He did this work of looking at results of pediatric oncologists in the team, and he looked at the PIP, so not the waivers request. We are talking about a product for which at least there is one indication potential in children.

We had 18 active substances, 9 new, 9 authorized, so 50-50, and 15 which were really anti-oncology products. The 3 remaining were supportive. And for these 18 products you had actually 8 written requests already.

[Slide.]

These 15 active substance, purely oncology product, convert to 52 indications, 24 had an indication purely in adults. There were 26 conditions covered, so corresponding to 15 front-line treatment and 15 relapse treatment, and 2 of these conditions were covering the range from adult to children.

I hope it is not too complex, but numbers are always difficult to explain.

[Slide.]

In terms of class or condition waivers, we have published a number of oncology conditions. There is more now, but just to see that, you know, it is no surprise to see these conditions that is waived in principle.

[Slide.]

Now, I would like to show you that we are probably meeting exactly the same issues as you are when discussing this development in children, what to do when there is a very low incidence or prevalence of the disease.

You want the dates are, you know the children are affected, how can you make a good development, have enough data to be reassured, to have less uncertainty. This is a difficult issue because you are putting also a burden on the company. Sometime some condition may not be studied because it's not feasible.

[Slide.]

Also, if we look at the condition, from our perspective, looking at the condition in the broad sense, the broader the name, the more condition you include in it. If you take lung cancer as a condition, you have more than if you look at non-small-cell lung cancer, of course.

So, depending on where you set the limits, you can

have more potentially pediatric indication, which is what we are looking for, of course.

We had long discussion about what is a reasonable lower age range for studies in glioma, neuroblastoma, rhabdomyosarcoma, which is the appropriate cut-off, should we ask studies from the age of 6 months or from zero, from 1 year, 2 years and, when the company comes from trial for relapse or refractory disease in children, again, what is the age that we should set into the trial to include the patient.

[Slide.]

Also, in terms of trials, the content of the plans as we have seen them. We had already a number of trials which were completed, corresponding in general to the written request, all studies done by the companies, and we take them into consideration. They are not eligible for the reward but they can be taken into consideration.

Six trials were proposed or ongoing, which represented between 1 and 2 trial for active substance, and 6 of them were actually done through collaborative groups.

In the planned trials, there were, as you can see, mostly Phase 2, with a few on combination, and the company

proposed to do trials which were not included in written requests for only 2 cases.

[Slide.]

Just also a description or more specific about what we have seen so far, so you can see that certain indications are more frequently studied than others. But, as I said, we have just started, so it is still very early days. We may have a different pattern after 1 or 2 years of experience.

[Slide.]

We have many issues which are borderline ethical issues, what do we do when we have no corresponding development in adults, how do we get the proof of concept, how do we define what needs to be done in children.

We are coming end of Phase 1, how do we decide what is the good route for children. And we have seen so that most companies request a waiver for neonates. This is an issue because nothing excludes neonates from the need certainly, and also we recognize that trials are, of course, more difficult.

We also don't want to lead to a situation where all studies will be started at six months or one year.

We have high, different levels of information on the nonclinical data survey from companies. We have issues with the models sometimes of pediatric tumors, the choice of the study design. Very often the company says, oh, we will do the studies later, but they never tell us what they intend to do. So this is not for us acceptable.

[Slide.]

I tried to sum up in the table a little bit of difference between the U.S. on the European system. So that's where Mac sees that we have not understood how your system work. So, clearly, we have a mandatory system at the difference of the BPCA but more close to the PREA system.

Our instrument is not the written request; it's the Pediatric Investigation Plan. But in some ways it's similar in principle. The timing is different. The reward is very similar. The difference is because of our legislation, which doesn't make a difference between biology concern, chemicals. We have only one system which covers everything, but we don't cover medical devices. That is what is now included in the BPCA.

We include orphan drugs and at the end, the codes end is decided by a committee of experts, which meets only a

couple of days per month, which doesn't help us to work every day.

[Slide.]

Those are measures now. Many transparency measures, we were also concerned that some of the information obtained through the U.S. system was not reflected because the FDA did not have the power to get this information made public.

So, we published already the decision on the plan, so published a summary. So it's a lot of transparency for products which are not authorized. We published, not only the type of studies, the number, but also the timelines by which they are going to develop.

We will put the results when we have them in the product information, of course, and, as we do for NGO, that is not specific for pediatrics, we publish the basis for the approval.

[Slide.]

More striking maybe, we have an exhaustive database registration in Europe. It is mandatory in this database. It used to be confidential. But, for the pediatric trials--so any trial involving children from zero