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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Meeting of:

PEDIATRIC

SUBCOMMITTEE

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P R O C E E D I N G S (8:36 a.m.)

AGENDA ITEM: Call to Order.

DR. CHESNEY: Good morning. My name is Joan Chesney. I am in the infectious disease division at the University of Tennessee in Memphis.

I wanted to welcome you all to this historic first meeting of the Pediatric Advisory Subcommittee.

I think it is important to remember, and to enthusiastically thank the many consumers, consumer groups, pediatricians and pediatric organizations, including the American Academy of Pediatrics, who lobbied with great persistence and determination to have the legislation passed which has resulted in our being here today.

These organizations have also worked very hard to form the priority list of drugs, which I am sure we will hear more about today, called The List.

We all recognize that all growing children, particularly those who are premature or who have chronic diseases such as cystic fibrosis, diabetes, asthma, congenital heart disease and AIDS, absorb, metabolize and excrete drugs differently than the prototype 70-kilo adult male.

Until now, for 70 percent of available drugs, we have had to extrapolate from dosages recommended for a 70,000 gram adult to, for example, a 500-gram premature

infant.

We thank, as well, the FDA for forming a large pediatric subcommittee within the agency to address the many complexities of implementing the new legislation, and we very much look forward to hearing from many of them today, as they explain all the intricacies of the legislation to us.

Finally, and in advance, on behalf of children, we thank the manufacturers for working with the FDA to develop appropriate guidelines for pediatric drug administration.

We have a full and interesting day ahead. I would like to start by having the members of the advisory committee introduce themselves. Maybe we could start at this end of the table.

DR. MURPHY: Dianne Murphy, associate director for pediatrics at FDA, CDER.

DR. ROBERTS: I am Rosemary Roberts. I am the medical officer on the pediatrics team.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, Pediatrics.

DR. LUBAN: Naomi Luban, I am a pediatric hematologist and director of the blood bank at Children's Hospital, and professor of pediatrics at George Washington University School of Medicine.

DR. FINK: Bob Fink, pediatric pulmonologist, and

chairman of pulmonary and allergy at Children's National Medical Center in Washington, D.C.

DR. RODVOLD: Keith Roldvold, professor at the Colleges of Pharmacy and Medicine at the University of Illinois at Chicago.

DR. O'FALLON: Judith O'Fallon, Biostatistics, Cancer Center Statistics Director at the Mayo Clinic Cancer Center, Rochester, Minnesota.

DR. STOVER: Rhonda Stover, executive secretary, FDA.

DR. HUDAK: I am Mark Hudak. I am a professor of pediatrics at the University of Florida and chief of the division of neonatology there.

DR. FUCHS: Susan Fuchs, I am associate professor of pediatrics at Northwestern University in Chicago, and pediatric emergency medical, associate director, Children's Memorial Hospital, also Chicago.

DR. DANFORD: David Danford. I am professor of pediatrics, in the joint section of pediatric cardiology at the University of Nebraska Medical Center and Creighton University, Omaha, Nebraska.

DR. GORMAN: Richard Gorman, pediatrician in private practice in Baltimore, Maryland.

DR. NOTTERMAN: I am Daniel Notterman. I am a pediatric intensivist at New York Hospital in New York City,

and I am in the department of molecular biology at Princeton University.

DR. HORAN: Hi, my name is Michael Horan. I was invited as a guest today. I am representing PhRMA, the Pharmaceutical Research and Manufacturers of America.

DR. CHESNEY: Thank you. Rhonda Stover, our executive secretary, will read the conflict of interest statement next.

AGENDA ITEM: Conflict of Interest Statement.

DR. STOVER: The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such in this meeting.

In accordance with 18 United States Code 208, general matters, waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the committee's discussion of issues, and the development and study of all therapies in children relative to the implementation of the agency's new legislative and regulatory efforts to ensure adequate labeling and proper pediatric use.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A30, Parklawn Building.

In the event that the discussions involve any

other products or firms not already on the agenda, in which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interests of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

DR. CHESNEY: Thank you, Rhonda. Our first speaker this morning is Dr. Murray Lumpkin, who is the deputy director for the Center for Drug Evaluation and Research in the Office of Review Management.

AGENDA ITEM: Welcome and Introduction to FDA Pediatric Drug Development Activities.

DR. LUMPKIN: Good morning, everybody. Welcome to all of you who are here visiting today, and a particular welcome to all of you on the advisory committee.

As Dr. Chesney said, this is a historic day, particularly, I think, a very good historic day for those of us who are pediatricians and who have had, for many, many years as our main professional outlook, the betterment of children's health.

The idea that we actually, as a united community, both an academic community, a pediatric community here at

FDA, the pediatric community within the regulated industry, have come together in a joint effort.

Most of the times we get together as advisory committees, usually we are not of the same mind. This is one of the fun times where I think we really are of the same mind, basically, on what we are trying to do.

What we hope to be able to do during the session today is to help all of us look at these various initiatives that have come forward in the last several years, and try to figure out how we are going to use them for the betterment of children's health.

I am not going to spend a lot of time this morning, but I thought what I would do is perhaps take just a couple of minutes and think a little bit about how we got here and why we are here.

You are going to be hearing a lot more from Dr. Murphy and Dr. Roberts and Dr. Weiss today about the specifics of the legislation, the specifics of the rule.

I think it might be helpful again if we all, in the room, kind of thought about why we are here in 1999, thinking about children and children's health in the way that we are.

You know, for those of us who are pediatricians, I think if we are very honest with ourselves and think about actually what goes through our mind when we are taking care

of a child and we start to think, well, what would be the most appropriate care for this child and it ends up thinking, well, I think I need to have this child on a drug.

You start thinking, what is the basis of our decision. Why do we choose this drug, why do we choose this dose.

I think if we look back and we think about the choice of drug, the dosing regimen or the compounded formulation that we are having to work together with somebody to put together and think, why did we choose it, the question comes, is this from personal experience, is this from our own trial and error, is it because of advice from colleagues or a mentor?

Is it what we were taught when we were interns by someone who was taught when they were interns that this is the way you do it.

Is it based on anecdotal reports in the literature? Is it because we all -- I know I am dating myself here -- carried around our Harriet Lane and there was this kind of biblical approach, that this book in our little white pocket said this is what you are supposed to do and this is the dose.

As was mentioned earlier by Dr. Chesney, is it the fact that we have been extrapolating this from adult data and saying, gosh, I hope it works in the child when we do it

this way.

Are we looking at small, trending but really kind of inconclusive trials. At the end of the day, are the decisions that we make based on data from adequate, randomized, blinded, controlled, good scientific trials that let us do what we know is best for children.

Really, at the end of the day, what we are trying to decide is, when we take care of our children, are our pharmaceutical decisions based on bias, based on hope or based on science.

Again, I think if we are honest with ourselves, we would like it to be here, based on science. In reality, probably most of our decisions are based more on the first two characteristics here.

The question is, is this truly in the best interests of our children and is that what we want to do.

I think we all know -- and again, as Dr. Chesney pointed out this morning -- that if you take most of the drugs that are available in this country and you look at the approved package inserts, you find this statement: safety and effectiveness of -- choose your favorite drug -- in individuals under -- choose your favorite age -- have not been established.

We have ended up with the situation that approximately 70 percent of the drugs that are used in

American children today are not labeled for such use.

One would, of course, ask the question, why is this. How did we get to this situation. Why do we not think our children are worth better than this.

I think -- and, again, you will hear more about this from Dr. Murphy -- that if you go back to the mental thought processes that people were using, it is not that people were anti-pediatric or anti-child, but there were two major themes that kept coming forward.

One is, children are not little adults, and we would continue to agree with this. Children are different. You have to deal, as we all know, with changes in growth, changes in sexual maturation, changes in neuronal maturation, changes in the way drugs are metabolized.

So, we don't want to treat our children as what they are not. They are not little adults.

The second thing, children are not second class citizens. If we have an accepted scientific standard for putting drugs on the market for adults, why would we treat our children any less.

I think if you look at these, the idea was, well, children are different and children are not second class citizens.

We are not going to have a lesser scientific standard for them. Then, what do you need to do. We were

back in the situation, again, prior to 1994, where the general thought process was, in order to treat children in the way that we think they should be treated, one needs to do adequate and well-controlled studies in children.

While that is a nice thought, I think the reality is, people know what the difficulties are in conducting pediatric clinical trials, and this is not new to most of you who are here.

We know what the legal issues are, the IRB issues, the issues of consent and assent, the issues of using children as commodities, the idea of recruitment incentives and is this, in essence, really coercion in some situations.

Can children really consent for their children to be involved in a trial. The idea of clinical trial designs, what are the ethics of placebo-controlled trials in children.

How much adult data is needed prior to going into children. What are the power models dealing with populations that we know, in most situations, are going to be smaller than what we can have for adults.

We know the issue of the number of patients available at any time, the willingness of parents to consent to their children being in clinical trials, again, this mentality of not in my backyard. Yes, you can do it with other people's children, but I am not going to have my child

in a clinical trial.

The reality of laboratory methods in the past and the ability not to exsanguinate, or the situation where one was only exsanguinating children to try to get the kind of lab data.

Clearly, we have had a revolution in the technology and people can begin to address some of this.

The reality of the lack of appropriate formulations for children of certain age groups and, clearly, at the end of the day, the lack of commercial incentives and knowing that, at the end of the day, the corporations that make the medicines in this country are not charitable organizations, they are not designed to be charitable organizations and people don't expect that from them.

They have their own payrolls to meet, and there is a reality of trying to make something commercially viable to make it happen.

Well, these things simply did not exist in the past,-and the outcome was, as we all know -- and you will hear over and over again today the old adage that children are therapeutic orphans, that the reality is that we have a lack of standardized pediatric formulations for many drugs.

Because of that, people are having to extemporaneously compound them, and there are various issues

that go along with that.

The lack of adequate data to support dosing efficacy and precaution statements in labeling when people use it, and the concern on the medical legal liability side, about these labeling disclaimers, as they were, in labeling and promotion, despite the fact we are all aware of the widespread use of these products in our children and use by ourselves.

So, in this decade, people began asking, very appropriately, saying, does this have to continue.

I think most of us believe, in our community, we can do better by our children than what we have done in the past.

The issue has been, how do we get people to focus on this. How can this become an issue that the larger pediatric community, the industrial community, the academic community, the regulatory community, can focus on this to see, can we change this culture.

What do we have to do. Clearly, what we have done in the past and the hopes that we have built in the past have not worked, and this became a public policy issue.

This is not just a science issue. It is a public policy issue of how do we take the revolution in science, the revolution in technology, put it in our public policy hat and change a culture that has not served our children

well in the past.

As you know, it began in 1994. It went through the change in our pediatric labeling initiatives at that point in time. It went through the FDAMA legislation. It went through the pediatric rule that was recently published.

I think what you are beginning to see today is the culmination of people trying to answer those questions, the public policy questions and the science questions of, how can we do better by our children.

My bias on this is that one hopes that in this five-year period that we have the exclusivity, in the next period of years, that we will see -- and I think we are already beginning to see it, we are already seeing numbers of requests to do pediatric studies coming in.

We are hearing about already the saturation of the pediatric research infrastructure in this country. People have, indeed, begun to respond to the public policy initiatives that are underway.

I think what you are seeing, and the fact that you are all here today, is witness to the fact of a real heightened partnership between academia, between industry, between the regulatory parts of our government to really address this issue head on, to end up at the end of the day with quality pharmaceutical products that our children can use, that they are not having to be compounded with goodness

knows what.

We can develop really good scientifically-based information so that parents can believe that children are being treated based on good data, so that those of us who are practitioners of pediatric medicine can make good decisions that are based on good science, not on anecdote, not on hearsay, not on what our mentor told us because his or her mentor told him that, as we go forward into the future with our children.

Now, we at the agency take this very seriously. This has been something that particularly those of us who have a pediatric background have been very, very interested in for a long time.

We take it so seriously at the agency, as many of you aware, that we have created an office within my immediate office of pediatrics.

I have asked Dianne Murphy, for this year, to become the associate director for pediatrics. As many of you know, Dianne is a pediatrician herself.

She worked at the agency back at the early part of this decade in the antiviral world. She has got an infectious disease background. She is a virologist by trade.

She left the agency in the early part of the decade and became a professor of pediatrics at the

University of Florida.

While she was down at the University of Florida, she continued to serve the agency wonderfully as a member of our antiviral advisory committee.

About a year and a half ago, I was lucky enough to convince her to come back to the agency in the capacity of office director for ODE-4(?). As you know, ODE-4 is the office where most of our antimicrobial divisions are located.

Not only wearing that hat, as the pediatric initiatives began to heat up, she began to take on the role of trying to coordinate, on a daily basis, the implementation of the 94 rule of the FDAMA provisions, of the 98 rule that just went into effect.

As you can imagine, this was like two full-time day jobs. It got to the point where it became quite clear that we needed to have a focus to spend the entire amount of time on her day job and most of her night job working on pediatrics and trying to implement this. Dianne was gracious enough to agree to do that.

She is going to be your FDA leader through this day. She is the person who is primarily responsible at the agency for the implementation of all of our pediatric initiatives. I know she is going to do a good job helping you guys get through this.

Again, let me welcome you here today. I am extremely pleased that you are here. I think this shows that we are committed, as a joint pediatric community, to doing right by our children.

I think at the end of the five years, or as we go on further into the next decade, that we will be meeting together many times to discuss many special issues -- ethical issues, scientific end point issues, things that we are really not had to deal with in children in the past because of problems we have had in the past.

It is an incredible future. It is a very, very bright future that I see for us as a community and, clearly, for our children.

What I would like to do now is introduce you to Dr. Murphy, for those of you who do not know her, turn this program over to her, and I wish you a very good day. Thanks very much.

[Applause.]

AGENDA ITEM: Pediatric Regulatory Initiative History.

DR. MURPHY: As Dr. Chesney and Dr. Lumpkin have said, this is a very exciting time and a lot of work has gone into it. We are going to review, again, some of that today, where we have been, because we think it is very important to understand how we got to this day, as we enter

a new millennium, that we will not enter it treating children with drugs the way we have in the past, as Dr. Lumpkin clearly outlined we have been doing for a while.

The committee plays a critical role in this process, and it is clearly designated in the rule, that this external advisory body needs to exist to help all of us through this process.

We expect that they will be a resource for all of us as we move forward.

Today's meeting is not really, although it is the inaugural meeting of the pediatric advisory subcommittee, it is a little different from our usual advisory committee meeting, in that we do not have today, before us, a specific product to evaluate, only a program to implement.

Our goals are a little different for that reason. We won't be voting up or down at the end of the day. Our goals today are to provide information to prepare the committee and all of us for this future task.

We wish to make transparent how FDA plans to implement the legislative and regulatory driving activities behind the pediatric drug development program.

A goal is to seek questions and comments as input, as to how we are implementing the legislative and regulatory aspects of this program.

This slide is going to become the theme slide,

which you will see and hear many times. During this slide, I was going to go over why children are therapeutic orphans, but Dr. Lumpkin has really very well covered the many reasons that have been offered for why it has been difficult to study children.

I think one thing that we need to get out on the table is, we know it is difficult, but it is worth the effort. We have to do this. I think we have all come to that conclusion.

The reason is that we have had a number of misadventures. There have been numerous instances where children have suffered because products have been developed and put out for use by children without information.

This was a soothing product to help children who were irritable and crying. The problem was, it had a lot of morphine in it and a number of children died because of this product.

We had another product, sulfanilamide, a wonderful drug, the wonder drug at the time in the 1930s. They needed an antibiotic. They needed a formulation for children.

They developed the formulation for children, when the children would accept. As we all know, they don't always swallow everything we ask them to take. We often see it back again.

So, it had to be something that children wanted to

take. It had to be sweet. So, they found the perfect solvent. It just happened to be something like antifreeze and, in the end, 107 children and people died of renal failure, and the chemist who developed this solvent and formulation for children shot himself.

There have been, as I said, a number of misadventures as we tried to provide products for children.

This one, as you can read here, is thalidomide, again, a product that was out there and being used, and affected children in a way that was not expected, as many children were born with shortened forelimbs, because of the use of this product, not knowing the effects it would have.

So, the problem, it is, in 1999, true that there is inadequate information regarding pediatric use for almost three-fourths -- we will go through today a little bit about how this number changes, but in essence, you can say three-fourths of prescription medication.

As Mack indicated, we don't like trying to decide the dose in this situation. We shouldn't have to be calling the company, FDA or anybody trying to find out what other information is known about how to dose down to this age group at this point.

It has been a long haul, trying to get to where we are today. These are, I call them, the pediatric labeling bench marks.

We are going to walk through them again this morning, because I think it is important to see how we got to where we are today. Again, Dr. Lumpkin touched on some of these points.

We are going to start with the 1977 American Academy of Pediatrics Committee on Drugs statement, work through what the FDA did, thinking it would help solve this problem, then what we thought we had done to help solve this problem, and then where we hope we are, finally, at a solution today.

As Mack alluded, in 1977 there was, if you will, a milieu that you should not study children. It was unethical to submit children into experimental trials.

You still have that concern, that children -- all the concerns that Mack mentioned about enrolling them in experimental situations.

What the American Academy of Pediatrics panel said in 1977 is that it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled, experimental situation every time we prescribe.

What information do we get? How do we know that adverse event? Is it reported to anybody? That is what we have been doing.

It is not only ethical, but imperative that new

drugs to be used in children be studied under controlled circumstances so the benefits of the therapeutic advances will be available to all who need them.

The other side of this is that maybe we will be less hesitant as we learn more about how to use these drugs, to use them in this age population.

So, FDA issued, in 1979, a regulation that said, if you are going to have a statement in our label about using a drug in children and it is approved for adults, that children are no less citizens -- as Mack pointed out, they are not second-class citizens -- that you should have substantial evidence derived from adequate and well-controlled studies, unless the requirement is waived.

So, not only should you study them, but we are going to have the same level of efficacy criteria that will be applied to children, which, in usual terminology, is two adequate and well-controlled trials.

That is what we said. We are going to fix this problem by asking that children be studied and we are going to bring this data in.

Well, bob for the apple, but you don't always get it. In this situation -- that was 1979 -- we looked at things in 1990 and were no better off in our labeling for children, providing information in the label, how do you use these therapies in children, than we were in the 1970s.

So, FDA then proposed, in 1992, that we would hope to help the situation. We had a lot of input from industry, academia, various types of clinicians, how can we approach this problem. What is the issue here.

We came up with this statement in the prologue of this proposed regulation: We are hoping to codify criteria which will make manufacturers more aware of how feasible it is to get pediatric information in their labeling, show some that they may already have adequate information at their disposal to do so.

We actually found this out over the years, that often there is information out there that is available.

Show others that the evidentiary threshold is not as great as previously believed, and encourage all to pursue better pediatric labeling for their drugs.

The final regulation has two important concepts in it, and we will just keep hammering on this, because it is a fundamental construct with where we are going with the 1997 and 1998 regulation.

If FDA can conclude that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations that we can extrapolate adult efficacy data, you don't need to repeat the efficacy trials in children. So, this is the standard that one needs to reach.

So, the rule applied to drugs and biologics. It did say, however, that once you made that decision, you would need to provide us some other supporting information. This supporting information is what is missing, how do you dose it, do children react differently, what are the different adverse events they may be having.

We need that additional information. So, it is defining a different world of studies in a way, if you can make that first assumption.

I just wanted to mention about that different world of studies before I go to this slide, that we are talking about dose ranging, studies so that we can find the dose, pharmacokinetic studies so that we could find the dose, pharmacodynamic studies where we think the link is there but we are not quite sure because, as we are discovering as we go in to ask for these studies and companies are coming forth with their proposals, they and we are discovering we don't know exactly what end points should be sometimes.

We are needing to develop that, and sometimes you need to do a PK PD link study versus an efficacy study. Sometimes you just have to do the efficacy studies because we are not sure of some of the information as we go forth in developing these end points.

As I said, safety, always safety, always looking

for that data.

So, what was the result of the 1994 effort to provide additional information on how to use therapies in children? It was not good.

We ended up with 77 percent of the submissions to the agency that had no improvements in the labeling.

Why did this occur? There was an option. The option was that you could put in the label that safety and efficacy in children has not been established.

Unfortunately, that was the option that many chose. However, we did receive 65 applications which provided information to allow us to adequately label all ages, and another 35 that provided some information, but not all the age groups in which we knew that therapy was being used.

We still were at a point of not having the information that we needed. In addition, in 1997, the agency looked at what has happened over the last almost decade with new molecular entities. If we lapse into NMEs, that is what that is, or chemical entities.

With pediatric labeling between 1991 and 1997, the top line is, these are the new NMEs. Of these new NMEs, which ones -- the tag here of usefulness in pediatrics is that either we know they are potentially going to be used because they are in a class where they are being used, or

one would just expect they would be used in children.

So, 16 of the 30, 14 of the 25, so this is the line that we are looking at, products that should have had some information in them, and how do you use them in children.

This is the number that actually had labeling. We sort of peaked out. This is one of highest years ever, in 1991. Fifty-six percent had some information in the labeling.

Then if you go through, you will see that in 1992 it was 28 percent, 37 percent, 40 percent, 36 percent, 38 percent, 33 percent. They have actually gone back and done this in the 1980s.

The reason we picked 70 to 75 percent is that it varies, throughout the last two decades. That is the number of products that have labeling in them that we think are being used in children.

One of the other proposals is that, well, that is okay because we are going to do the pediatric labeling as a phase-IV.

As most of the people in this audience I am sure are aware, a phase IV commitment is a commitment to do a study after the drug is approved for marketing.

So, these are agreements between the FDA and the sponsor, that these studies will be done. This is looking

at the phase IV commitments for pediatrics between 1991 and 1997.

You can see that we really have a number each year, and this is post-approval, after that drug was approved, how many of the labels have had additional pediatric information put into them from the phase IV studies.

To be fair, we have had 70 promised and only 11 do we have in the label yet. It takes a while for these six to get into the label between 1991 and 1997, but even if we took this six and put it down here, the discrepancy between the 70 and the 17, I think, is evident.

So, that brings us through where we have been. In the last 18 months, we think some fairly remarkable things have happened. We want to review that with you this morning.

The person who is really going to do the heavy lifting this morning is Dr. Rosemary Roberts, who is a medical officer in anti-infectives and who has also, now, committed her time to the pediatric program and initiative, and will walk you through this morning the implementation of the Food and Drug Modernization Act and the pediatric rule.

This is a slide to say we are now moving forward.

DR. ROBERTS: Good morning, and again, thank you very much for coming today to the inaugural session. It is

my privilege here to march you through the two major approaches that are ongoing within the agency right now, and that impact not only us in the agency, but certainly impact industry and academia as well.

The first approach is the modernization act and then, more recently, the pediatric rule.

Now, what are the key elements in these? The modernization act is voluntary and it provides an incentive if the studies are done according to our request and in an established time frame.

The rule, the studies are required to be done, and it has been designed to sort of fill in the gaps that are left as a result of the modernization act.

Now, the modernization act, FDAMA stands for Food and Drug Administration Modernization Act. It is a law. It was passed by Congress and signed on November 21, 1997.

The section of this act that is pertinent for us today is section 111.

The biggest thing here is the carrot, the incentive. It provides six months of additional marketing exclusivity.

I can recall, and I have heard people say subsequently, six months, is that really going to be much of a carrot.

Well, as we go on you are going to see that it

must be a carrot to industry, because there has been a lot of activity and interest expressed by industry since the guidance was put out, as to how they can qualify.

Now, the implementation process that the agency put together based upon the legislation is this. The statute says that the agency must request the studies.

So, the agency must issue a written request for the pediatric studies. The studies that are then submitted by the sponsor, in order for them to qualify for exclusivity, need to be responsive to the written request that they receive.

How do we make up this written request? It is based on the assessment of what studies are needed to produce a health benefit in the pediatric population.

What is missing. What information do we need to adequately label this product for its indication or indications, that are relevant to the pediatric population, so that the physician who is prescribing it knows how to use the product, knows what the safety concerns may be.

Now, this is a big responsibility, to issue these written requests. So, we wánted to share it by industry and, actually, we wanted to put it back on them.

If you are interested in studying a product and qualifying for exclusivity, we want you to submit a proposal to us.

The guidance for industry that was published at the end of June 1998 identified about 15 points that needed to be addressed in a proposal, that we would then look at and use, hopefully, as a basis for issuing a written request.

Now, as many of you in the audience know who have gone through this process, sometimes what you get back from us reflects some of your elements but not all of them, and there may be many things that we have added in addition to what you submitted.

Also, the agency can, on its own initiative, issue a written request, independent of the sponsor.

Now, as I said, there has been lots of activity in this arena. If you recall, from the slide on the 1994 response, we had 100 labeling supplements of the 400 that led to some information being placed in the labeling.

That was over about a three-year period of time that industry responded.

This effort has been going on in earnest for the last nine to ten months. We have had 109 proposals submitted to the agency since July of last year.

To date, we have acted upon 63 of those proposals. Forty-nine have had written requests issued. The other 14 were felt to be so inadequate, that an inadequate letter was sent back to the sponsor, oftentimes with suggestions by the

divisions as to what information needed to be included.

The other thing I wanted to point out is that not all divisions are sharing in this burden equally at the agency.

The biggest areas of interest and activity have been in the cardio, renal, neuropharm, also the antiviral area and then the anesthesia/critical care area.

Some of the divisions have had very little activity at all, and that may be a reflection of the types of drugs -- this is reproductive and neurologic.

In the anti-infective area, old antibiotics don't have any exclusivity to attach to, so there hasn't been a whole lot of interest there by industry.

Now, this is the list of approved drugs for which we have issued written requests. It does not mean the studies have been conducted or submitted. It doesn't mean they will ever be conducted. This is just the list of the approved drugs that the agency has issued written requests for.

What I would like to point out is, there is a variety of conditions already for which written requests have already been issued.

There is abavir for HIV, there is atrovastatin as a cholesterol lowering agent, cromolyn sodium for asthma, buspirone for anxiety disorders.

We have got anticonvulsants, fever control, fungal diseases and we have got antihypertensives.

Other drugs for asthma, we have got a drug here for treatments of the symptoms of rheumatoid arthritis, and a combination product for the treatment of hepatitis C.

As you can see, there is a large variety of conditions that are being addressed in the written requests that are out.

Only time will tell as to whether those studies will be conducted and we will get good labeling for these products, but hopefully, we will.

Clearly, the tide has changed. We are seeing a lot of interest by industry. All these written requests were sent out in response to a proposal by industry. So, they have expressed an interest in doing studies in the pediatric population.

Now, we went back and we looked at 44 of the written request letters and itemized the types of studies that are being requested.

- Overall, there are 31 efficacy studies, 32 PK studies, 7 PK PD studies, and 15 safety-only studies. There are six other studies which are outlined on the next slide, which would be, for prophylaxis, there were a couple of studies that were OTC actual use studies requested, and then there are studies that are a combination of efficacy, safety

and pharmacokinetics.

What ages have been included. Well, we are very happy to say that we are getting some studies that are going to involve the very young infants and the neonates and even one that is going to involve the preterms.

Then, clearly, the concentration here is in the two and above area. For others, I point this out, because those categories that were initially defined in the 1994 rule, zero, the neonatal period, zero to one month, then one month to two years, two to 12 years and then 12 to 16 years, are very arbitrary categories.

If you have had a chance to read the preamble to the final rules, it says there clearly that those were arbitrary, and that we intend to be flexible.

As you can see, by these various other groupings here that are involved in some of the studies, clearly, those arbitrary age groups don't always fit.

One of the things that the divisions and the sponsors who have sent in proposals have to wrestle with, what is the appropriate pediatric population that we should be studying.

Where do we need the benefit, based upon the physiology of the child, based upon the disease, based upon how we know the drug works, what is an appropriate group to be studying.

As you can see, there are a lot of permutations here. Neonate to Tanner stage 3, we have three years old to adolescence, and a lot of combinations. So, you don't have to stick to those arbitrary age groups. What you need to do is have a scientific basis upon which you select the appropriate population for the studies.

Then, this is the carrot, this is the incentive that industry is looking for. To date, we have granted exclusivity on five products and there are three pending review.

Now, in addition to the incentive that the legislation mandates -- I mean, the incentive that is provided by the legislation -- the other thing that we need to do is to report back to Congress as to what was the success of this program.

The legislation clearly outlines what we need to report back to them by January 1, 2001, the effectiveness of the program in improving information about pediatric use and approved drugs.

- Was the incentive adequate, the economic impact on taxpayers, consumers, on generics, and any suggestions we might have for modification.

So, as we are implementing this program, we are also implementing ways to collect this data, and preparing the report back to Congress.

This is extremely important, that we are able to report back how this program worked, or where there might be gaps that still aren't being covered.

You have heard about the first approach. Now I am going to move to the regulation. This is not a law; this is a regulation and, as I said earlier, studies are required under this.

I put this up to remind me to remind you that the regulation covers new and marketed drugs as well as biologic products.

The legislation really does not involve much in the way of biological products. The reason is that most biological products don't have any exclusivity or patent protection to hook onto. Therefore, there is no incentive for them.

However, under the final rule, biologics are covered and are joining us in this effort, and training their people just as we are training ours, in how to implement the rule.

Now, why the final rule now? Certainly, this has been asked. There are incentives out here. Why don't you just let the incentive play out and then not go forward with the final rule.

Clearly, the incentive appears to be working, as we just discussed. However, there are certain limitations.

There are gaps in what can qualify for exclusivity.

Things like antibiotics, old antibiotics which have no exclusivity to hook onto, the biologics we just referred to, drugs that are already off patent, or older products that no longer have exclusivity, these are gaps.

They are not going to be able to qualify for exclusivity because they have nothing to hook that six months of marketing exclusivity to.

In addition, FDAMA is voluntary. They don't have to do the studies we have requested. There is a concern that there will be drugs, age groups and indications left unstudied, where there is a relatively smaller market for the product or if the studies that are needed to be done or are requested are in neonates or the young infant, where it is technically more difficult to do studies.

There is no guarantee, once the studies have been conducted under the modernization act, will actually lead to improved labeling.

For this reason, it is appropriate to have the regulation at this time.

Now, the scope of the regulation is new drugs and marketed drugs, just as the scope of the modernization act. New drugs here are defined as new chemical entities. New indications except orphan indications are exempt from this, new dosage forms, new dosing regimens and new routes of

administration.

Now, for marketed drugs, although the rule does apply to marketed drugs, it applies to it only after we have given the exclusivity a chance to play out.

This is very important. Congress has mandated that industry has the right to this. We want to let it play out. So, for marketed drugs, we are only going to require it for marketed drugs when there is a compelling need.

That is defined as a drug or biologic product that offers a meaningful therapeutic benefit, and the absence of labeling would pose a risk or, for a product where there is substantial use in the pediatric population and the absence of labeling would pose a risk.

So, these are the only times that we foresee we will require studies under the regulation for marketed products. We do intend to have the exclusivity incentive play out wherever it can.

Now, for new drugs, the default is that pediatric studies are required, provided the product will offer a meaningful therapeutic benefit or substantial use.

Now, since it is a new drug, not labeled, the absence of labeling criteria has been deleted from this definition.

Now, meaningful therapeutic benefit actually comes from the priority definition within the agency. However, it

does not mean that you will get a priority review for the supplement when you submit it. That is a decision by the division at the time.

Meaningful therapeutic benefit is defined as a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products adequately labeled for that use in the relevant pediatric population, or the drug is in a class of drugs, or for an indication, for which there is a need for additional therapeutic options.

Just as in adults, we want to have a variety of products available to treat a condition. We want the same for children.

One child may react to something and another child won't. One child may respond to something that another child won't.

It is important that we have options for children for the treatment of various conditions.

Substantial use has been defined in the regulation as used in more than 50,000 patients for the labeled indication.

Now, the waiver criteria. The regulation went into effect April 1 of this year and there are three options that the division has now as they send out approval forms for applications in house.

One is to say, the studies aren't done, and if you think you are going to qualify for a waiver, then send in a justification for a waiver.

What might be the justifications that we might waive pediatric studies on the application before us?

It might be that the product does not meet the criteria for meaningful therapeutic benefit and substantial use, if the applicant could show that the studies are impossible or impractical to carry out.

If the product is unsafe or ineffective in the pediatric population, we certainly wouldn't require studies.

Then, for products where a special formulation would be needed, say, for the neonate or for the infant, and if the industry has made reasonable attempts to produce such a product and have failed, then a waiver could be issued for the population that needs that formulation.

There is a discussion this afternoon that goes into a lot more detail about the waiver process.

The other option at hand right now, since the rule just went into effect and, clearly, if we are taking an action on a product at this time, they may not have all those pediatric studies done. They may not even have started them yet.

So, deferral is one of the things that is an action that is likely to be going on for products that are

currently being acted upon.

One of the reasons to defer is that the new drug, for adult use, has gone through the approval process and it is ready to be approved, and the studies aren't done.

We will not hold up the approval for a product that is effective in the adult population because the pediatric studies are not done.

What we will do is defer the studies, but we will specify a time that those studies should come in.

The other reason we would defer the studies is if there is some kind of a safety concern or something that has come out in the development program for the adult product, and we want to see additional safety or effectiveness information in the adults before we move forward with pediatric studies.

As I said, the rule went into effect April 1, 1999 and now all applications, at the time of the approval, must either have the required studies or have met the waiver criteria as previously outlined, and will be discussed this afternoon, or have agreement on deferral with a specified date as to when the studies should come in.

Now I am going to hand this back to Dr. Murphy, who will talk to you about how these two integrate.

DR. MURPHY: We are a tag team. One of the reasons that I am back up here is that we have changed the

agenda a little bit also.

We understand the committee has some need to end by 4:00 o'clock this afternoon. Therefore, we are going to move future considerations, which was after 4:00 o'clock, up to this morning. Hopefully, we will move fairly quickly and still get through all of our topics.

How is this going to happen? That is really the question everybody has. You have these tools now. I think Dr. Roberts has done an excellent job of walking everybody through them, and how do we see them interacting with each other.

The integration of the pediatric rule is important, because it is stated in the rule that this will become a regular, routine part of FDA's drug development activities.

This is not going to depend upon either that the division has pediatricians, or they remember to think of this, or that there is a very active interest.

This is going to be part of the questions that every-division is going to ask when an applicant comes in with their proposals for how they want to develop a product.

We are going to say, what is your pediatric drug development plan. That is a tremendously important change that the rule mandates that we have happen.

The rule even tells us when. It says, at the end

of phase II for non-life-threatening serious disease, that the sponsor will submit one month before the meeting -- because these are routine meetings that we have with industry, so that we are all on the same page, if you will, on how a product is being developed and where everybody is, that we have an end of phase II meeting.

Before we have that meeting, the rule says, the industry will send in their packet their pediatric drug development program.

Now, it may be that this product is for prostate cancer. It would be perfectly reasonable that that plan says, we feel that this therapy is not appropriate for pediatrics and we are requesting a waiver and these are the reasons why.

Theoretically, or at least the rule states that hopefully, by the end of phase II or between the end of phase II and the pre-NDA meeting, FDA and the sponsor will have determined whether the product development plan will waive pediatric studies and, if not, there will be a plan as to when these studies are going to be coming in.

That is going to be determined by multiple factors such as other information, safety issues, need, et cetera.

Again, for serious and life-threatening diseases, we have moved that process up to the phase I activities.

The rule also says that at the pre-NDA meeting we

are going to review -- part of the process, the regular, routine process is going to be, we are going to review the status of pediatric studies.

If the sponsors run into some difficulties, then this is the time that we need to know that, and we need to know, where they didn't think they were going to need a deferral, that they may need a deferral, and we need to work out what the plan is.

This is, again, a tremendous step forward for all of us, and we look forward to having these discussions with the sponsors.

The sponsors will be notified about the possibility of exclusivity for FDAMA. If we keep saying this over and over again, it is because there has been so much anxiety out there, that somehow the rule is going to overwhelm FDAMA and we are just going to go out there and require studies and not pay any attention to the law, which would sort of be not a good idea.

What we want to say over and over again is that we will address the possibility. We are taking it to the point where we are putting it in our form letters when they submit an application.

The rule says that we will be requesting pediatric studies. Please look at your possibilities for exclusivity. Those will be in the form letters that go out.

At the time of approval, the approval letter will state -- we put this up because right now there are products that are already so far along that there is not an opportunity for us to have discussed this potentially at the prior stages.

We have now put in our approval letters this statement so that sponsors will know that, yes, we need studies, we are going to defer them until this date, and please evaluate your potential for exclusivity.

So, we are saying -- this is, again, one of our goals -- how we are going to implement this. We are going to implement this so that, at every opportunity, we discuss both tools, many tools, how we are going to approach getting the information that we need to be able to provide the correct dosing, identify the particular safety issues that may be associated with using these drugs in all pediatric age groups in which they will be used.

There are some differences here that we wanted to point out, because it is becoming confusing. FDA cannot require submission of pediatric studies under the pediatric rule, until December 2 of 2000.

Now, that doesn't mean we can't discuss it or talk about the drug development plan. That just means that we can't require those studies to be submitted to us.

However, does that mean that studies won't be

submitted to us? What we are seeing is, already, studies are currently being requested and received under the modernization act, because they are coming in requesting exclusivity.

So, you will hear people state, that is for the rule, that we can't require submission, but we certainly will be talking about them. As I said, many of them are already being planned.

Many pediatric studies are already being planned and, as you saw from the data, we have already granted exclusivity for studies that have been submitted. So, some studies are coming in.

Finally summary, again, under the rule studies are required. You need to evaluate the need for pediatric information on only the drug product and indication being reviewed at the time that that application is in house, versus FDAMA, the studies are voluntary, you evaluate the need for pediatric information on the entire moiety.

You may not have an application for other products with that moiety, but you can ask for the studies.

Then incentives only where there is an underlying patent or exclusivity protection.

Again, under the rule, we have meaningful therapeutic benefit based on the priority definition that Rosemary went over with you.

Studies are not required for orphan indications under FDAMA. Additional information that may produce a health benefit is the definition versus meaningful therapeutic benefit. There are slight changes in the wording here.

Incentives do attach to existing orphan exclusivity.

Just reiterating the differences in dates, under the rule, we cannot require the studies to be submitted. There is no sunset date.

Under FDAMA, as of November 21, we have been requesting studies for submission, and this legislation has a sunset date of January 1, 2002.

So, you may be asking, so what. We think it is pretty revolutionary and there is a lot going on, but the committee is nascent. What does this have to do with me, and why am I here.

AGENDA ITEMS: Future Considerations.

DR. MURPHY: We are going to move to the future considerations talk. The rule says that the FDA will convene a panel of experts including at least one industry representative, and seek its advice on a range of issues related to implementation of the rule.

This is where the role of this committee will be important, as we move along in our implementation of both

FDAMA and the rule.

The rule clearly states that it sees as possibly these are topics that may come before the committee. I am going to go over each one separately and discuss them.

This slide is just to show you where we are going to go for the next six slides, and we discuss what the rule has identified as potential issues that may come before this committee.

The committee will provide annual oversight of the implementation of the rule. Ladies and gentlemen, that means that you will be here at least once a year, and my estimate is that more likely twice a year, because we are supposed to look at waivers.

We will look at the general product areas for which waivers have been granted. We will look at the appropriateness of the application of criteria that Rosemary mentioned in granting these waivers.

We will be looking at the deferrals. The status report is basically how many deferrals, what type of products, and the timeliness of the submissions that were deferred.

We were discussing ethical issues which have occurred in clinical trials with pediatric patients. As Rosemary indicated, we have already issued a number of written requests.

As we review these proposals, we know that certain issues are already occurring.

Should we ever study children who don't have the disease. Should they be randomized to a placebo. The bar is higher, as Dr. Lumpkin indicated this morning, when one is involving people who cannot give their assent. Assent is different from consent.

There is a burden upon us to ensure that these trials are implemented in the most ethical way that they can be.

This actually has not come up yet, but it is often discussed, reimbursement. These two issues have already arisen.

It states that we will review trial designs and data analysis. There is some confusion about, what is the pediatric committee could to do? Is it going to usurp the other committees for antivirals or cardiovasculars?

The answer is no. However, there can be combined meetings. This committee is seen as a resource for this rule, regulation and policy and how it is going to be implemented.

We feel that you will be able to contribute to some of these issues as they come up for trials in children. As I mentioned, we are discovering how much we don't know or how much we need to change end points in some of these

activities.

So, discuss general principles of drug development in children, might be an issue, the disease states, the design issues.

By that I mean, we may want to look at how many times have we assumed that the disease is the same in adults and children, and that we can extrapolate the adult efficacy.

As you saw, Rosemary said that 32 efficacy trials have been requested, but the rest are not. We made that assumption.

We probably need to go back -- I think industry would be very interested in this, too, to go back and look at when we have made that assumption.

Has it worked? How well has it worked? When has it not worked? Why has it not worked? Have we underpowered some of the other studies or what? What is going on.

Review the need for additional therapeutic options. That has been alluded to this morning, that we need options for children, too. If anything, they react more diversely than adults, because of the tremendous physiologic changes that are going on in the entire age spectrum.

We may need to look at how many therapeutic options we do need. A general update, though, will be

required to look at where we are in product labeling as a result of these initiatives, and when are therapeutic options sufficient.

We don't expect we are going to arrive at this for a while. We have a long way to go. We can almost say, gee, wouldn't it be nice to get to there. We don't see that happening any time in the immediate future.

This is stated in the rule, too. We will recommend marketed products to be studied. Dr. Roberts covered this for you, I think, fairly well for when we would do this.

This is under the rule. When would we require a marketed product that is out there to study children. Only when there is a compelling need, exclusivity has been ineffective or not applicable.

How will we do it? We will do it with all the stakeholders. There will be an open public forum. This committee will be part of that forum.

It will involve the sponsors. It will involve the clinicians involved in these trials, or use of these products.

We are trying to tell you that this will be not done in a quiet manner. It will be a public discussion.

The American Academy of Pediatrics is developing a list of products that they think are actively used in

products, and there are other lists, different from the list that we are talking about today, but lists of products that people think need to be studied.

Last, this committee is to provide oversight on the progress of studies. Circumstances for delayed initiation of pediatric studies.

I think we will learn what are the difficulties, as we go forward in implementing these studies. That is something that I think will be important general knowledge information.

So, we are going to do all this. The committee is going to be involved in all this. We had better be prepared to report to you.

We do know that we have to report to Congress, as you heard. We have some reporting requirements already laid out for us.

We are going to attempt to do this by being able to report to Congress on the number of written requests issued.

In other words, as you heard this morning, how many proposals have been sent in, and then how many of the requests has FDA been able to issue that we think studies are needed. What types of studies, you had a preliminary look at that this morning.

What information has been incorporated into the

labels. This is very important. Are we going to go through this whole practice, if you will, and end up with nothing in a label?

I can foresee, if that happens, FDAMA will sunset. We don't want that happen. We would hope that we will be able to gather this information and put it in the label and have it meet the public health need that has been identified.

We need to talk about what economic impact FDAMA has had, and by that, they are addressing the issue of delaying generic products for six months.

In addition, we have to be able to provide an updated priority list by May 20 of each year. You will hear more about that later. We have to review waivers and deferrals, you have heard about that. How are we going to do all this? Examine the reasons.

We do have a pediatric tracking system. It has been evolving from our earlier days in 1994 when we had a pediatric page. It was literally a piece of paper that went around with the application.

We actually have entered the computer age and this is all computerized. We are able to collect from this system the number of pediatric proposals, the number of written requests, the lengths of time to issue of the written request.

One of the things we are hearing from industry is, we want to do this, we are ready to go, you guys are holding us up. We can't get you to answer that proposal.

We do have that response. We admit, in these early phases, it took a while. Some of the written requests did take more than four months to get back out again.

Remember, the divisions have to go into their information base, make sure what is already there, what things need to be added, where that product is throughout the agency -- remember, it is the active moiety -- and then decide what studies need to be done. Do they agree with what was proposed.

That whole process was new for everybody as far as a response and how we responded, and we now have a goal of 120 days to respond.

Sometimes there are scientific issues that have to be answered before we can respond, and some of those may take longer.

One of those, I know, had to go before another advisory committee before the division could answer the questions about this type of study.

As I indicated earlier, it is going to be very important. People are going to want to know what is it that we actually had to do to get this information. Are all the age groups being covered.

Again, the numbers of waivers, what categories are the waivers in, what are the reasons they have been waived, and the deferrals, average length of deferral.

Why are we tracking all this? Because the ultimate goal is label changes. The ultimate goal is that the label will provide the practicing physician, health care provider, the information they need, so they aren't standing there, either at the bedside in the ICU and knowing they don't have any information and how are they going to get it, or the general pediatrician, many times a day saying, there is no information on how to dose it under 12, but we are going to do it on a per kilo basis, extrapolating down.

We will be assessing how many labels have been changed and what information has gone into them, and how many do not.

We hope, when we reflect back upon all of this, that this will be well done, and that we will all be celebrating what we have done for children in this process.

To find out more, you can go to this internet side, which FDA has guidance and information, publication of products, approved products that you saw Rosemary put up, where there have been written requests. There is a fair number of things on that list.

We are also going to -- at this time we are going to go forward and have Dr. Weiss give us a discussion of

clinical trials.

I thought, before we did that, what we actually thought we would do is move her discussion to after the break and allow the committee to ask us questions.

I want to tell the committee that, if you don't ask us questions, we have questions for you. We have five sample cases that we can work through, just in case this is so clear that it is mud.

If you have questions, we will work through most of that, and that will be fine. Rosemary, Leanne, Karen, please be willing to kick in -- Monica -- if the question is beyond my ability to answer and you feel you have information that you can add to these questions.

DR. CHESNEY: Let me start. I have many questions here, but I will just ask two to begin with. The first one is very fundamental. Could you explain the difference between legislation and regulation.

My second question is, what if the date for pediatric study completion, after you have already given permission for the adult form to be marketed, what if the date for the pediatric completion is not met.

DR. MURPHY: We very handily have Leanne Cusumano, who has worked as a lawyer, worked very intimately in the whole process of developing the regulation and helping us implement FDAMA. I think this is a perfect question to punt

to Leanne.

MS. CUSUMANO: The first question is actually a good one. I guess asked it a lot of times from a lot of different kinds of people.

When you are talking about laws, both statutes and regulations are laws, and they carry the weight of the law. Statutes, which is what pediatric exclusivity is based on, are passed by Congress. That is where pediatric exclusivity comes from.

A regulation is an agency's interpretation of a law passed by Congress. So, the pediatric rule is based on FDA's statute saying that it has the ability to require studies for the safe and effective use of drugs.

They are just different levels. If you are talking about a court deciding how much weight to give one over the other, the court gives more weight to something passed by Congress, to language in a statute over what an agency's interpretation is, but they are both laws and they both have to be complied with.

Your second question was about, what if the pediatric studies that are required under the pediatric rule are not submitted by a date specified in a deferral.

We hope that doesn't happen. We want everybody to submit their pediatric studies. If there is time necessary to do those studies, that is reasonable. If there are issues

related to that, they should come back to the agency and talk to the agency about the problems they are having in completing those studies.

What turns out as a deferral might turn into a waiver or a partial waiver because you can't develop a formulation, or you have done recruitment and you just can't get enough patients to power the study properly and it is not going to tell you what you need to know.

If, after all of that, or if a sponsor is totally non-responsive to the rule, FDA would have to look at the situation and see, how important is it to have pediatric studies, do we really need these studies.

Basically, that product is out there on the market and it is adulterated and misbranded. It is something we take to a court and ask a court to probably take that product off the market until they submit their pediatric studies.

Then it would be in the hands of the court. If they don't do that, they would be in contempt of court. There would be fines, possibly jail time, who knows what. I mean, that is an extreme situation.

Obviously, the starting point is that we want to work together and we want to get the information into the labeling that needs to go into the labeling.

DR. CHESNEY: Thank you. Do others have questions?

DR. GORMAN: A large number of the products that are used in day-to-day practice have long since lost their exclusivity under FDAMA. I will use amoxycillin as an example.

How does the agency see approaching the pharmaceutical industry to get those studies? Will it be a single manufacturer or multiple manufacturers, the organization?

Who does the agency approach under the rule to get appropriate labeling for those agents?

DR. MURPHY: Well, the first part I will start and then I will get to the difficult part. Suppose the manufacturer of amoxycillin wants to change anything as far as the scope that you saw of that list, an indication, a timing, a regimen.

If they want to do that, and they submit an application, it would come in under the rule, and it could be any one of the people who are producing, because you are talking about the generic producers.

So, whoever comes in with an application would then come under the rule.

Now, we have said that we would try the approach of asking the various producers to approach this in a cooperative way. I think we have been told that may or may not happen. That is the other approach that we have

contemplated, that we would approach all the makers of that product and ask them, or tell them, these are the studies we think should be done, and how can we get these studies completed and submitted.

I don't know if anybody else on the team has any other additions to that, but that is the approach that we have for right now. We will have to see how it works or does not work.

DR. GORMAN: Since there seems to be so much activity under FDAMA, is there any mechanism that has been considered by the agency to find a way to provide an incentive for industry to do that, as has been done by new drug entities, or entities still under exclusivity.

DR. MURPHY: You are talking about those that don't have exclusivity.

DR. GORMAN: Correct.

DR. MURPHY: Is there a way that we could provide an incentive to those products that do not have exclusivity.

I was not here for all those discussions, although I can-tell you there has been a lot of thinking about that. People want to make this something that everybody would want to do.

Right now, I don't think anybody has come up with an alternative way. We can't create exclusivity for those products at this point. Leanne, I don't know if you have any

other comments to add to that.

MS. CUSUMANO: This goes back to the point about the distinction between the law and the regulation. For the agency to be able to do something, it has to be based on a law Congress passed.

There is no authority for FDA to say to drug manufacturers who don't have existing patent or exclusivity, that we are going to grant you exclusivity. There is no law that allows us to do that.

What you are talking about, it would be something that we would have to go back to Congress. That will probably be part of the results of the report, when we report to them January 1, 2001. What have we gotten labeled, what is still missing and why.

DR. MURPHY: I think this report will be very important.

DR. EDWARDS: For someone who has conducted a large number of trials in children, it is frequently difficult to enroll patients in trials, as we all know.

Is there any attempt by the agency to network with other groups, advocacy groups, to help them understand the importance of this legislation, to foster greater recruitment and a sense of helping with this goal and what are your plans, or is that something that is not an FDA initiative?

DR. MURPHY: We have a couple of activities going on. I am sure there are many more that we need to consider.

One of the things that we have been trying to do -- and just so you will all know, this is an unfunded mandate as far as FDA, there are no user fees, pediatric studies were excluded.

We have tried to go out to as many groups and speak to them about how we see this and how we plan to have it implemented.

Dr. Kathy Rogusu(?) is in charge of our communications group. Jeanette Locklear is the person who is coordinating our speakers activities.

We have a tremendous interest in this, and we could just quit reviewing products and go out on speaking tours right now. We are trying to, in essence, modulate our activities in that field.

In addition, we have been working with the academy and hope that they, too, will play a role in making this information available.

We meet with PhRMA to discuss this and hope that they will help us in communicating what is going on here.

We will be speaking at the DIA drug information meeting in June, where many of the sponsors will be. But as far as the academic part of it, we have spent speakers to subspecialty meetings -- we have to be very careful.

If we start adding up how many subspecialty groups -- so we are actually hoping the academy will have a place for us in one of their meetings where we can go through all of this.

We are working with the pediatric pharmacology research units, as far as making sure everybody understands where we are going with this.

There is a group that has met once or twice called the alliance, which involves PhRMA, AAP, USP, FDA, to discuss how we are going forward with this.

If you have suggestions for an efficient way in which we can make this information available -- we are putting a lot of it on the internet -- please let us know. Rosemary, have I forgotten anything?

DR. ROBERTS: No.

DR. HORAN: Could I just add something to that? I recently met with Patty Delaney of the FDA, and she and her colleagues are working on cancer, not just cancer for children, but cancer for everybody.

Among the things they are trying to do is, in working with the NCI in their PDQ data base, they are trying not only to become the bastion of information for cancer patients and children, what they should do, but also to provide them with any relevant pertinent clinical trials in which they might wish to enroll.

If that whole system were to expand, it might possibly expand to all areas of illness, not just cancer.

Along similar lines, two weeks ago we had two visitors at PhRMA from the Inspector General's office. Usually when you hear that you say, oops, you know.

They actually sometimes do independent studies on their own. They had been hearing from investigators that, gee, we have such difficulty in recruiting patients.

They also had heard from patients, too, you know, we have this disease, we really want to find out about trials but we can't.

These two people were just at the beginning of their investigation. They said, which is true. They must both be true.

So, the Inspector General is developing a report for the entire issue of clinical trials. I don't know how successful that will be, but if it sparks interest and gets things going so that we have much greater information about clinical trials that are available and how you can connect and get into them, that would be very good for medicine in general and, hopefully, in this particular situation, pediatrics in particular.

DR. MURPHY: If we could develop something where the ACTG trials are, other large trial groups have been able to make information on how to enroll in studies, possible

biomechanisms like this, that would be a tremendous benefit to everybody.

DR. FINK: With the definition of substantial use at 50,000, is the intent, then, to define any use under that as falling under the orphan disease classification, or will there be a gap between orphan disease classification and substantial use?

DR. MURPHY: Leanne is shaking her head. Do you want to try that, Leanne?

MS. CUSUMANO: It is definitely not the intent to change the number for orphan usage. What is it, 200,000 for orphan use? There is actually overlap the other way.

DR. MURPHY: We never like gaps. One last thing, too, is that again, it is not an or situation in there. If there were less than 50,000 but it was going to provide a meaningful therapeutic benefit, it still would be something we would wish to pursue -- might be. It is not an or in that situation.

DR. FINK: If this initiative is successful in generating labeling changes, what is the plan to re-educate pediatricians in terms of FDA guidelines.

Most pediatricians barely open up a PDR because they are so used to not finding useful information there.

DR. MURPHY: Oh, stab. Again, I think it comes back to the issue that Dr. Edwards was bringing forth, which

is how do we communicate with pediatricians, and not just pediatricians, family practitioners who, under our new health care system, are seeing a fair number of children also. How do we get this information out.

I think we have to say that we are going to rely tremendously upon many of the professional societies to help us in getting the word out, that these labels really do have useful information for children in them.

I know people say, gee, they are such small print and they go on forever and ever. Actually, they are getting longer, particularly in HIV. We actually give you the clinical trial results in the label. That is a tremendous resource.

You don't have to go find the article, look it up. The clinical trial results are right there in the label.

I guess my message would be, give the label another chance. We can't do anything about the print right now. Please start looking at them, because we are putting what we think is more useful information in the label.

DR. WEISS: I also want to say that sometimes, when labels are changed, there are dear doctor letters that go out to practitioners. Oftentimes that is a better way to catch one's eye rather than actually having to say, gee, is it time to look at the labeling and see if anything has changed in that god-awful small print.

Certainly we do that when there is new safety information but even sometimes when there is new prescribing information. That is just another mechanism that could be out there.

DR. CHESNEY: I have another question, and this is partly to be sure I understood correctly. If a company does request exclusivity, which I understand may not happen, but assume a company does not want exclusivity.

They are not required until December 2, 2000 to do pediatric studies. If that is the case, it really only leaves one year before you have to present the results to Congress in January 2002. Am I correct about those dates?

DR. MURPHY: Correct. Basically, if somebody doesn't want to submit a proposal and thinks that they are eligible for exclusivity, then FDAMA, whether it progresses or not, we will not get those studies before we are going to be reporting because they are not going to do them.

That is one of the things we will be looking at, is what was the non-response to FDAMA.

Under the rule now, we may have studies that are coming in under exclusivity, but in essence, the report to Congress is, what was the effect of exclusivity.

It is going to be hard to say sometimes but we will have some overlap, a little bit of overlap, but the rule requirement really, in a way, allows us a little bit of

a window where we can see what that response is. Am I making that clear?

DR. HORAN: As a follow up to that question, isn't it also possible that the FDA, in conjunction with advice from this committee, may decide that that particular drug or the indication was kind of marginal to begin with and, so, may choose not to worry about it.

DR. MURPHY: Absolutely, that will be part of the whole assessment. If someone did not apply for exclusivity or we did not request it and some people think that it should have been, then there will have to be a discussion as to why it wasn't and why we don't think it should have been.

DR. EDWARDS: The ethical questions that you raised are really very complicated and difficult ones. Is there currently an ethicist who will be working with this committee, or perhaps on this committee already?

I think in previous committees that I have participated in, their input is amazingly helpful.

DR. MURPHY: Absolutely. This is one of those ironies that we hate to make public, but do you know where all the ethicists are today? At an FDA meeting somewhere else in the country.

There is an ethicist on the committee, someone whose background is in biopharm. Not everybody could make this meeting today who is on the committee.

A little further response to that is, when we have that meeting, which I anticipate we will have, we will also be augmenting the committee with additional resources that we will want to have come to that meeting.

DR. DANFORD: I don't have an understanding yet for exactly what the rule, as it stands now, does if there is no compliance or incomplete compliance when data is requested.

The background for the question is that, although I think that we are going to get a lot of very good information about many drugs with this effort, I do sense that there is an impasse that might be reached for many drugs, due to the tension between the doctors and their current prescribing practices and the public health, scientific view of life.

Pediatricians, in particular, have become accustomed to working under sort of a lack of knowledge or minimal knowledge, and we kind of do our best and scale the doses like we think they ought to be scaled and say, well, we have got to treat this disease somehow, this is the best we can do.

They have become accustomed to a somewhat lower standard than we might expect, were we developing a new drug from scratch.

They have been prescribing drugs for their

patients using that somewhat lower standard, convinced the patients that the drugs are good for them as being prescribed.

All of a sudden they are going to be asked to participate in a double blind, placebo-controlled trial of this medicine that, hey, we thought was good all along.

Are we going to have trouble recruiting patients to participate in trials in sufficient numbers in a substantial subset of drugs from we might, from the public policy scientific sense of things, really want that information but not be able to recruit the physicians or their patients to participate. If that happens, what does the rule do?

DR. MURPHY: Wow. Let me see if I can extricate a couple of thoughts here. One is that, we will never dictate the practice of medicine. No matter what information we get into the label, it will never cover all situations. I think all of us understand that.

Physicians will always have times in which they are going to have to practice off label. I think that we recognize that.

We want to provide the most best information, so that you are not making any more jumps than you have to, for when you feel like you need to do that. For pediatrics, as you have heard, there is a huge void in this area.

The next thing is, with our patients, will there be a disconnect that, we have been practicing all these years. Now why are we enrolling them in all these studies.

I think when you enroll somebody in a study, you have to be answering a question. The question may relate to the science is evolving, that we are finding out that cytochromes are maturing at different rates and gut enzymes are maturing at different rates.

We know we have more probata water composition during certain times and some things are distributed more in water than in fact.

Is it not absorbed in this age group because of the enzymes. Is it distributed differently. Is it metabolized differently.

Are there reasons that some of the drugs have different adverse effects in adults. Is it really because children are reacting differently, or they had the incorrect dose, or we could use a lower dose.

One of the things that we have found, certainly, I think, in HIV work is that more sometimes was not better, and that you may be able to use a lower dose.

I think that we will be able to enroll -- we hope people will be able to enroll -- because it will be based on a question that you are answering, that we think that there is a reason, because of the changes that are occurring, that

this drug is not absorbed, metabolized or eliminated, because of whatever organ is different at that age group.

To just say, oh, we have to go study all kids in an age group because we don't have that data, I think that we would not.

I think if we think absorption, distribution, metabolism and elimination are the same, we will make that extraction from adults to a certain age range.

It is just where the specific age ranges are that we are beginning to try to address. Certainly, I think we all recognize that in the neonatal area. We have many changes going on.

I don't know if that answers your question. The best I can say is that, the way you enroll people into studies is, they want to help answer the question, so there has to be a good question.

DR. HUDAK: Dianne, there are obviously a lot of drugs on the list.

DR. MURPHY: The priority list.

DR. HUDAK: The priority list, and it is a bit daunting to go through that list, in fact. There are many drugs on that list -- for example, my experience in the nursery is that they have been studied in the nursery since being released and there may be information in the literature that has been provided by various investigators

in various institutions across the country and other areas of the world.

Pharmaceutical companies probably do not have that information on reposit. Nonetheless, it is good information. We often guide our dosing decisions in the nursery based on some of that published information.

How is that information going to be made available to the FDA? Should it be made available? Can you comment on that?

DR. MURPHY: Again, Leanne, tell me if I misspeak here, but as far as our approach to literature, what we are asking is that you submit the data, not just the articles.

If there is information out there, you would work with the sponsor in saying, we think this is important information; we want to get it in to the FDA.

If they can do it through exclusivity, fine, if they can get the data in to answer the questions. But it can't just be a literature submission for that. It has to be clinical studies.

MS. CUSUMANO: To expand upon it, that is true for pediatric exclusivity. There has to be a clinical trial which, in the Secretary's discretion, may include a PK study such that that is a clinical trial.

So, a literature search alone is not sufficient for that. But you are talking about getting information in

the labeling separate from the pediatric exclusivity issue.

That was the intent of the 1994 rule. What we said was, if there is information out there in the literature, file a labeling supplement, let's get the information into the label. We saw that that wasn't very successful, unfortunately.

What we are finding now, with pediatric exclusivity, and probably will also find with the rule is, you don't have to do new studies to fill in those gaps on the labeling.

We are not going to ask you to do new studies. We are going to ask you to pull the information together and file it, so that it does get in the labeling.

DR. MURPHY: Okay, good.

DR. HUDAK: So, in other words, pharmaceutical companies may be going to investigators who published a paper in search of the data to present to the FDA, even though the studies weren't done under the sponsorship of the pharmaceutical company at the time.

DR. CUSUMANO: That is right. There is no requirement for pediatric exclusivity that the sponsor have conducted or sponsored the study.

DR. WEISS: Let me add, just in terms of using literature based views for applications, it has been done and I think will continue to be done. It is not an easy

process.

There are standards that one looks at to just make sure that what is published is truly, in fact, what actually happened. It is always difficult when you don't have the primary data in hand, as well, to verify things.

There are sources and criteria set out. Actually, the agencies published a guidance to industry in providing clinical evidence of effectiveness, that actually sets out some of the criteria that can be used to rely on published literature as evidence of effectiveness.

So, it is certainly something that people should take advantage of and look at, and see if that could be applicable.

DR. MURPHY: Again, though, because you started off with the priority list, there are some nuances when one is applying for exclusivity, as the end point of that.

DR. NOTTERMAN: In light of the response to the previous phase IV initiative for pediatric labeling, I just wonder if you have a feeling or sense of the number or proportion of entities for which deferral is contemplated, at least in the early years of implementation.

DR. MURPHY: In the early years, we would anticipate that the majority will have some deferral. The reason is that, in some of them, the process has not occurred. The product is ready to be approved.

As we have stated, we are not going to hold up an efficacious therapy for adults to bring the pediatric studies in.

Because we have, again, another one of those gaps, we anticipate that that is going to happen. However, a deferral has a time date in it. What Leanne was describing to you, though, is that there is a tracking mechanism now to look at this. We will be reporting. It will be very public.

If you have a deferral, you are supposed to be doing studies and you haven't brought them in, it is going to be a very public discussion, that this isn't occurring.

If there are good reasons for that, as we have talked about, that is fine. Those will be public, too. We hope that this will be a cooperative discussion on why things aren't coming in. Again, that was that sixth slide.

We are supposed to publicly review the progress. I think the word in the rule was the timeliness of the submission.

DR. CHESNEY: Thank you very much for answering our many questions. Dianne, let me ask you, should we take a break now until 10:45 and then hear Dr. Weiss, or did you want to review some of the cases that you had prepared for us.

DR. MURPHY: I think we ought to get it over with,

if it is all right with everybody. We don't have to go through all of them. I think we could just do a couple of them, if you want to quickly do that.

Our first case -- again, Leanne, you had better come back quickly if we have questions related to these. We are all learning, too, and continuing to learn.

A sponsor is development a new molecular entity which will have use in both the adult and pediatric population.

They have presented their pediatric drug development plan at the end of Phase II meeting. At the pre-NDA meeting the sponsor stated they will be on target and expected to have two of the three planned studies ready to be submitted with the NDA.

Their questions are: They want to know what they need to do to qualify for the additional six months of pediatric exclusivity.

In addition, they state they would expect a deferral at the time of approval and are asking is that likely.

Don't go to the answer yet. What has to happen if they are going to qualify for six months of exclusivity? Yes, they must have received a written request and the studies they submit must be responsive to the written request that they submitted.

In addition, they state that they would expect a deferral at the time of approval and are asking, is that likely.

The second one, the deferral would be granted for the incomplete -- we call it that, but it is not really. It is a study that we are anticipating is not going to be done in time for the NDA application. A deferral would include a date by which the last study would be submitted.

Any questions about this? Okay, next page.

The sponsor submits an application to the FDA for an NDA for an indication that exists in both adults and children.

Pediatric dose and safety information is part of the submission. The FDA states that the submission is sufficient to comply with the 1998 rule. Does the sponsor also qualify for an exclusivity extension?

Same answer, folks, only if. Submitting data to satisfy the rule does not automatically result in exclusivity.

The type of information required for exclusivity may be different, because remember, it is the moiety, not just the product. So, that data that they submit must be in response to a written request.

A sponsor submits an application for an NDA to the FDA for an indication that the reviewing division determines

does not exist in children.

The reviewing division grants the sponsor a waiver from the pediatric requirement of the 1998 rule. Remember, Rosemary told you that this would have to happen for every product that comes through, one of the three actions.

The sponsor submits a proposal for pediatric studies for another indication to another division.

Can the division that received the proposal -- in other words, the second division -- respond with a written request for pediatric studies to qualify for an exclusivity extension?

So, the contrast that you see here, hey, they got a waiver from one division and now they are coming in to ask for exclusivity.

Yes, if there is a determination that the information would provide useful information. If the report satisfies the terms of the request -- in other words, the division, the sponsor, we all agree that for that indication there was information we wanted, and we issued a written request.

The sponsor submits an application for a disease that is not generally thought to exist in children. This is something else that is occurring. A disease that is diagnosed for adults is now being questioned whether it exists in children.

The disease, however, is not one of the conditions that automatically generates a waiver. We don't mean automatically. We will be discussing waivers later on today.

Can the sponsor get a waiver from having to comply with the 1998 pediatric rule anyway? Go ahead and go to the answer on this one.

Probably, but the sponsor must request a waiver and submit supporting documentation providing the basis for granting the waiver.

The FDA could determine that older children, such as adolescents not be excluded, and could grant only a partial waiver.

In other words, there may be parts of this age group that should be waived but not all of them.

The last case, a sponsor submits a supplemental application for a new indication for an approved therapy. The original application was granted a waiver on the basis that the approved indication does not occur in children.

Is the new supplemental application exempted from having to address the 1998 rule due to the previous waiver.

No. A waiver is granted for an indication in a specific population. It is not granted for the product. A new supplemental application invokes the rule. If the sponsor wishes, there is also the possibility of submitting

a proposal to qualify for exclusivity.

The point is, there may be a waiver in one situation that wouldn't apply in another situation, and exclusivity may apply in that situation.

There are a lot of activities or approaches that may apply to any one product. I think sometimes the confusion, people have three different sets of facts and if you just change one of them, it sort of changes the answer.

That is our sample cases, to walk through how one goes through some of the decision making in implementing these two activities.

Joan, did you want to take a break now? I just want to go ahead and introduce Dr. Weiss before she comes up because I won't be back up here.

Dr. Weiss is the director in the division of clinical trial design and analysis, Office of Therapeutics in the Center for Biologics. After the break, she will be speaking to us on lessons learned from pediatric drug development programs.

We didn't want to leave this morning thinking that there was an absolute deficit. There are obviously a lot of people who have done research and studied therapies in children.

We wanted to talk about what were successful approaches, because we are going to look at those as we go

forward. Then we will go into comments from a number of, I think, the academy and PhRMA and consumer representatives.

Thank you all very much for you attention this morning.

DR. CHESNEY: Thank you, Dianne. We will take a break now and reconvene at 10:50, 10 minutes to 11:00, for Dr. Weiss' presentation.

[Brief recess.]

DR. CHESNEY: Dr. Weiss is our next speaker and she will be discussing lessons learned from pediatric development programs.

AGENDA ITEM: Lessons Learned from Pediatric Development Programs.

DR. WEISS: Good morning again to everybody and welcome to this first inaugural meeting. Again, I also, on behalf of the Center for Biologics, want to extend my welcome and appreciation to all of you for participating in this important advisory committee.

As Dianne said at the close of this morning's session, because of all the prior discussions, the 1994 regulations to improve labeling in pediatrics, which wasn't particularly successful, with the passage of the modernization act of 1997 and then the FDA regulations of 1998, there is clearly a message that there is more that needs to be done.

What has been occurring in the past hasn't been adequate or successful and more needs to be done.

We also didn't want to completely walk away with you having the impression that nothing has been done in pediatrics.

Most of you well know that there have been products successfully studied and marketed in pediatrics. So, that is the object of this presentation.

I just want to make my little disclaimer. I use the word drugs all the time in my talk because it is too cumbersome to say drugs and biologics.

Being that I am from the Center for Biologics, I am not excluding the products in my center. I mean, when I say drugs, I mean both drugs and biologics every time.

So, what kinds of products have had successful drug development programs for pediatrics. This is not a complete list.

My criteria to make the slide was, everything that I could think of, just off the top of my head, that could fit on one slide with a font that was large enough to be able to read. There are probably many, many more examples that all of you can think about.

Whether you consider things by product class or by disease specific type of category, there are many, many types of drugs and biologics out there for pediatric use,

from the preventive strategies, the vaccines that Dr. Edwards is very familiar with, to large other classes of agents, anti-convulsants, oncologics, immunosuppressives, et cetera.

Then when you look at disease specific types, many, many antibiotics labeled for otitis media, for meningitis, common disorders like asthma, atopic dermatitis, as well as for the rare diseases, such as chronic granulomatous disease or Goucher's disease.

So, if we think about some of the drug development scenarios and what we consider when we think about success, this is just a very simplistic version, where a sponsor identifies a drug as having potential utility in pediatric patients.

It is either something that is developed specifically for pediatric use, such as the vaccines or perhaps some of the blood replacement products that Dr. Luban is very familiar with, or it is something in the course of development, serendipitously, that is identified as having some potential utility in pediatric patients.

Then the sponsor goes on and evaluates the drug for safety and efficacy in pediatric patients, and we have heard that there are a number of different ways that that can be done.

Then, ultimately, the drug is marketed with

appropriate labeling for use in pediatrics. That is the sort of standard scenario for success.

There is another one that needs to also be considered, which is the converse, where the drug is identified as unsafe or potential unsafe or ineffective in pediatric patients, either because it has actually been studied in pediatric patients and this information has been obtained, or there are other signals from other sources of data and then that particular drug is not studied or, if it is not studied, it is not marketed, and labeling appropriately reflects that type of information.

So, among the different types of lessons that one needs to consider when thinking about pediatric development are what kind of data the FDA and sponsor will consider when determining whether, or even when, to initiate pediatric studies.

The kinds of information -- and this is a very incomplete list as well -- the kinds of information that goes on in one's thought processes when thinking about whether or when to initiate a pediatric development program, involves certain disease or condition-specific factors, whether or not there are other treatments, for instance, or preventive strategies that are available, the effectiveness of those treatments, the specific toxicities of the treatment.

Is the particular type of drug in a class, such as for AIDS or cancer, where there is just a crying need for additional types of therapies in that area.

Then there are data from our animal toxicology program that might help sort out this information, for example, the reproductive toxicology, carcinogenicity studies, genotoxicity studies and, when appropriate, studies in juvenile animals.

Then, of course, if there is prior human -- and generally this is going to be adult data -- that certainly needs to be factored into the equation.

So, these are a couple of examples that I have of when the preclinical data have been useful in considerations for pediatric trials.

I have on the slide two case, two drugs. These happen to be two drugs for HIV infection. In one, it was found in the animal toxicology studies that there were problems in the reproductive toxicology, the segment three, which is particularly the types of studies done where animals are dosed with an agent during pregnancy and then through lactation and then you look at the second generation.

In this particular product, there was found to be impaired cognitive function in the offspring. Again, these were, I believe, rodents and they had difficulty going

through mazes or things that rodents are supposed to be doing.

In addition, the genotoxicity testing was positive. In this particular case, there were also prior human data which revealed a particularly disturbing toxicity, that of peripheral neuropathy, which was quite severe and quite problematic.

The result of that was that pediatric trials were felt to be not appropriate, at least at that early venture, and were delayed in the drug development process.

The second example is another drug for HIV infection, where all the animal toxicology data were all quite clean.

The upshot was that pediatric trials were commenced early in drug development. In fact, the very first studies that were done with this particular agent included more pediatric patients than adult patients for HIV, which is a real rarity.

Another case that probably many people on this committee are quite familiar is the example of the quinolones and the preclinical data that factor into one's risk/benefit assessment.

This is a particular class of antibiotics where there have been findings in the animal toxicology program of bone and cartilage abnormalities in young, growing animals.

Because of this particular finding, which is always a concern in terms of studying agents in children, the effect on growing developing bone as well as effects on immunologic development, sexual development, et cetera, because of this finding, evaluations of pediatric populations have been limited to only those patients who have serious or life-threatening diseases, such as patients who have cystic fibrosis or pseudomonas infection, patients on cancer chemotherapy that have neutropenia and fevers associated with their chemotherapy, where the risk benefit was felt to be more appropriate.

This is also an example, too, where there are many, many other antibiotics that have a better safety program, the idea being that those antibiotics are the ones that should be used first, and these only reserved for more serious conditions.

In addition, there are probably class warnings on all quinolone products that indicate this particular toxicity.

The next area I want to go into is one you have already heard some mention by Dr. Lumpkin and Dr. Murphy this morning, which is the extrapolation from adult trials to pediatric patients.

This is a very important area. It was the whole basis of our 1994 regulations. What you have already seen,

but I think it is worth just reading this again, the regulations that were finalized in December 1994 basically allowed the agency to come to the conclusion that a treatment is safe and effective in children based on evidence of effectiveness derived from adequate and well-controlled trials in adults when the agency will have concluded that the course of the disease and the effects of the drug -- both beneficial and adverse -- are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. That is kind of a mouthful, but I think it is stated quite well.

This is something that, again, was finalized in 1994, and is reaffirmed in our 1998 regulations, that when these conditions are met, the agency will consider that information and not require the repetition of full-fledged efficacy trials in pediatric patients.

Exactly what situations are applicable to this particular regulation is not always all that clear, and I think that is going to be some of the discussions, perhaps in the future with the advisory committee. It is something that we go through all the time, when we consider what types of pediatric data are going to be needed for an indication that is already approved in adults.

A particular case study that we have on this,

which goes through the evidentiary standards that were used for making this extrapolation is a particular drug which was already indicated for the treatment of partial seizures in adults, as well as pediatric patients down to age six.

Extension of the labeling to pediatric patients, to infants down to the age of one month, so basically for treatment of infantile seizures, was accomplished by basically meeting the criteria of the 1994 regulations, establishing the similarity of seizures regardless of age, the similarity of response to treatment.

Many of this type of information, these types of data, were obtained not only from the adult data, but also looking at in vitro data.

The similarity of disease, interestingly enough, in this particular situation, was also helped, not only by the large body of scientific knowledge that said abnormal activity of neurons is the same, regardless of age, but also by biopsy material from parts of the cortex that were resected at surgery, probably for intractable seizures, and actually examining the pathology in the various ages.

The similarity of response to treatment. There was already an existing body of evidence that indicated that this particular drug resulted in quiescence of seizures when a particular level was reached. That was regardless of age.

Then, a dosing regimen that resulted in plasma

levels in the therapeutic range. In this particular situation, there were already pediatric studies that were done, but these were studies that were actually not adequate to demonstrate efficacy of the product on its own right.

However, those data gave us a lot of information about the regimen that was used, and the fact that that regimen resulted in plasma levels that consistently were in the therapeutic range.

That was a range that, in vitro, was able to halt the seizures or halt the neuronal excitivity.

There was the fact that there was also an acceptable safety profile, and that, again, came from the information in the clinical trials, which were not appropriate for establishing efficacy, but certainly gave us a lot of comfort about the safety. That was an example.

The next lesson that I want to talk about is really not a final lesson. I think this may be more of a lesson.

Efficacy measurements in pediatric studies is something that we struggle with all the time. I suspect that this committee is going to be thinking about these issues in subsequent meetings.

It is an issue about when alternate outcome measures to demonstrate efficacy should be explored.

When there are situations where it is not

acceptable to extract efficacy from adults, the criteria that were previously mentioned cannot be satisfied.

Either you can't be certain the course of the disease is the same, or the outcome, or the treatment is going to be the same.

Then it is going to be a requirement that studies with clinical outcomes will be necessary in order to have pediatric labeling.

However, for many situations it is impractical, if not impossible, to measure the same clinical end points that are done in trials in adults or older pediatric patients, and there are a number of examples. Many of you can think of other ones.

For instance FEV-1, some of the trials of asthma, requires a certain amount of cooperation, and it probably goes down to the age of five or six, perhaps, at the lowest.

You can't really have a very young child cooperate with the tests that are required for pulmonary function. Or it sometimes requires a pediatric patient to understand written and spoken language; for instance, a visual acuity scale that is commonly used in adults for pain assessments cannot be done in younger children.

When these kinds of situations are in existence, one needs to carefully consider what other alternatives can be used to measure efficacy.

Can there be modifications of the adult efficacy measures. There are many, many times where there are indices or scales that are in place, that are used to evaluate efficacy in some of the adult situations, such as for Crohn's disease, where there is a Crohn's disease activity index, or rheumatoid arthritis.

Many of these have assessments like having the scale to measure pain as part of those indices.

In some cases, it is possible to modify these indices, or these adult efficacy measures, to tailor them to be more appropriate for pediatric patients.

In fact, in the rheumatoid arthritis world, that is what is done. There is an index that is widely in use for adult RA patients, to evaluate efficacy.

There is somewhat similar, but not quite the same index that is used in juvenile rheumatoid arthritis, that makes it more applicable to pediatric patients, down to very young ages, probably down to age two.

Are new efficacy measures needed entirely? That is a difficult task, to come up with measures that then have to be tested and validated.

Are there potential surrogate markers that should be considered that need to be evaluated, hopefully, in early studies and validated.

Finally, is it possible, as Dianne mentioned

earlier this morning, to look at PK PD type relationships, and maybe use this as a measure of efficacy, instead of having to go to the full-fledged clinical kinds of end points.

Those are all things that are very, very difficult, and one where I don't think we have a large track record and a large data base yet in trying to come up with these alternative outcome measures.

The last lesson I want to talk about are the aspects of clinical trial conduct that are unique to pediatric clinical trials, that have to be in place in order to have a successful pediatric trial.

There are a number of things that, again, anybody who has been involved in evaluating pediatric patients in a clinical trial setting know very, very well.

One needs investigators with knowledge and training in pediatric assessments. That includes both efficacy type of assessments and safety assessments.

We hear over and over again that it is just not good enough to take a trial that is already in place for adults and just take the age range and extend it down toward the younger children, and then put it in place and have our adult colleagues or adult internists run the studies. It is just not going to probably work very well.

We need to have laboratory capabilities that are

in place to do things like run assays on very small blood samples, so that you don't come back and say, quantity not acceptable and you don't have the important measures that you need.

Many people are part of pediatric centers, so it is not an issue. But out there in the community, that is a problem.

During the design of a clinical study, one needs to consider the impact that it has on care givers. If there is going to be a lot of time missed from work because a child has to come in over and over and over again for evaluations, that might impact on the success of the trial.

There is going to be more than ever the critical role of IRBs in looking at issues of consent and looking at issues of assent, issues such as the amount of blood that is taken at any time, the total amount of blood that is drawn.

Again, this is all very commonplace for those who have been heavily involved in pediatric clinical trials for years, but these are somewhat novel as we start to implement the pediatric regulations.

We are going to see more and more of these clinical trials and the IRB is going to play a very important role.

There are a number of examples where the mechanisms have been in place for a large number of years --

decades -- that have allowed the successful implementation and outcome of trials in pediatric patients, the vaccine trial centers that Dr. Edwards is quite familiar with, the cooperative oncology groups that Dr. Luban knows well.

There are other areas where there aren't these very organized groups. There are a number of trials in pediatric infectious disease that are run successfully by HMOs, because they take into account all these types of considerations to ensure that they get the kinds of data they need.

So, in summary, there have been many examples of successful drug development in pediatric populations, success in pediatrics probably more so than in adult studies, but also relevant for adult studies.

They require the appropriate evaluation of the animal toxicology program and any prior human experience that is out there.

It requires consideration of the disease condition in adults and pediatric patients and knowledge of the metabolic pathways of the drugs, to assess whether or not it is relevant to extrapolate adult efficacy data down to pediatric patients.

It requires consideration of the unique aspects of pediatric clinical trials, of the use of alternative end points, and important issues of clinical trial design and

conduct. Thank you very much.

DR. CHESNEY: Thank you, Dr. Weiss. Our next speaker is Dr. Daniel Notterman, who is in the department of molecular biology at Princeton, and is going to provide us with some comments and input from the American Academy of Pediatrics.

AGENDA ITEM: American Academy of Pediatrics.

DR. NOTTERMAN: Thank you, Dianne. Good morning. I am Daniel Notterman, a pediatrician specializing in critical care medicine.

My clinical practice is located at the New York Presbyterian Hospital in New York City and, as you have heard, my academic base is at Princeton University.

On behalf of the American Academy of Pediatrics, I am pleased to be here today at the first meeting of the FDA's pediatric advisory subcommittee of outside experts.

This meeting was years in the making. It is fair to say that it is the result of tireless efforts of many pediatricians, both within and outside FDA, imploring, insisting and advocating to raise the standards of infants, children and adolescents, within the FDA drug review and approval process and, indeed, within the entire pharmaceutical community.

The results of these activities have been highlighted and summarized by earlier speakers, the passage

of a pediatric studies provision within FDAMA and the issuance of the 1998 rule.

It has been most gratifying for the AAP to observe the noticeable shift within the FDA toward embracing the pediatric population during the last several years.

When it comes to therapeutic drugs, children are clearly being given higher priority. We now stand -- the AAP and the FDA -- as true partners in moving forward this aspect of pediatric medicine.

Certainly the establishment of FDA's internal pediatric subcommittee of the medical policy coordinating committee, was instrumental in raising the visibility of therapeutic needs of the pediatric populations.

The most recent example of FDA's commitment to children is the establishment of the position of pediatric policy office within the Center for Drug Evaluation and Research, headed by a gifted pediatrician friend, Dianne Murphy.

It should also be noted that AAP has joined FDA in resisting the efforts of the generic drug industry in staying implementation of FDAMA.

The pediatric advisory subcommittee, then, is now underway. On behalf of AAP, I want to state passionately that this meeting and all subsequent meetings of this committee must be the catalyst for yielding concrete results

for children.

It cannot simply be a gathering of pediatricians and other experts to listen to presentations and have limited conversations.

The agendas must be task oriented, the debates must be candid, the meeting outcome must provide a recommended course of action to FDA.

We are pleased to note that today's agenda and today's comments so far indicate that this will be the case. They indicate that this will be an avenue to assist FDA in wisely and effectively making the difficult decisions that will benefit the population we are all here to serve, infants, children and adolescents.

I do look forward to a productive and substantive use of the expertise of this extraordinarily talented gathering of pediatricians and other experts.

AAP would like to take this opportunity to offer several comments and recommendations to guide the work of the pediatric committee.

- First, we are pleased that the role and activities of the pediatric advisory subcommittee will encompass issues related both to the 1998 rule and to implementation of the Food and Drug Administration Modernization Act, FDAMA.

The rule and the law complement each other, and can be applied in a synergistic fashion, to have more

studies done on more drugs, more drugs labeled for pediatric use.

The expertise of this pediatric committee should be used to ensure that both are successfully employed to the furtherance of children's health.

Second, FDA should utilize the energy and expertise of this pediatric committee in a broad, substantive capacity.

The committee could provide an essential understanding of the differences and similarities of a disease process in children at various stages of development and between them and between adults, and how this can translate to trial design. We just heard an excellent presentation on some of the essentials of this issue.

This body of experts should be relied upon to tackle the difficult but critical elements of pediatric studies, and of the implementation of the rule and the FDAMA.

When should waivers be granted? We view the issue of deferrals as a major substantive issue. AAP hopes that this committee will be able to monitor and review and provide guidance in the issuance of deferrals, and in ensuring that the pharmaceutical industry sticks to the time lines which are enunciated by FDA with respect to particular products.

Third, the pediatric advisory subcommittee should be relied upon to define what constitutes a substantial number of pediatric patients for a particular drug.

Within the rule, FDA has acknowledged that, while the operating definition of substantial number is 50,000 pediatric patients with a disease or a condition for which the drug is indicated, FDA has not codified that definition.

We have already had the beginnings of this discussion here, and AAP hopes that this discussion will continue in a robust fashion.

We feel that the pediatric advisory subcommittee has a central role to play in providing guidance to FDA regarding which drugs might need study, even when the pediatric populations fall below the 50,000 patient threshold.

Certainly, entities such as cystic fibrosis, cystinosis, hypothyroidism, arthritis and many of the dysrhythmmias are quite infrequent, but serious and sometimes life threatening.

Drugs commonly used in the treatment of these conditions in children need to be studied and labeled appropriately.

Inadequate or inappropriate treatment of such diseases may permanently harm patients, and we feel that these children also warrant better therapeutic options, even

when 50,000 patients are not affected each year.

Lastly, the AAP urges the FDA to include as part of the task of this pediatric committee the continued development and implementation of appropriate evaluation tools to review the advances made by the FDAMA law.

Prior efforts to increase labeling of drugs for children led to a trivialization of labeling changes, with the widespread use of the phrase, that safety and efficacy have not been established in pediatric patients.

Effectiveness of FDAMA and the rule must be judged by the concrete reality of the number of substantive changes in labeling, such as those that provide dosing guidelines for a new range of patients that accompany a new formulation for pediatric patients, or those that identify efficacy or lack of efficacy in pediatric patients.

The academy is grateful to all of you. I thank you for the opportunity to speak to you today. The American Academy of Pediatrics offers our continued support and expertise to you, in this important pediatric committee in the months and years ahead.

We are also pleased to place the considerable educational and pedagogic resources of the Academy of Pediatrics at the disposal of FDA, as it seeks to disseminate this new initiative to pediatricians.

In this regard, it is fortuitous, indeed, that the

October annual meeting of the Academy of Pediatrics is, this year, in Washington, D.C. We look forward to continuing our robust and instructive dialogue at that time. Thank you very much.

[Applause.]

DR. CHESNEY: Thank you, Dr. Notterman, for articulating so well the urgency that the academy and pediatricians have felt for many years on this issue.

Please thank the American Academy of Pediatrics for all of us, for all they have done in developing this legislation.

Our next speaker is Dr. Michael Horan, who is the associate vice president for clinical affairs of the Pharmaceutical Research and Manufacturers of America.

AGENDA ITEM: Pharmaceutical Research and Manufacturers of America.

DR. HORAN: Okay, thank you again. My relationship to pediatrics is not quite as extensive as the rather stellar cast that preceded me.

I got trained in internal medicine at Johns Hopkins, where I also did a residency in preventive medicine.

While I have not had any formal training in pediatrics, other than my six week clerkship at Georgetown University back in the 1960s, I have, in fact, since many of

the years I worked, I worked for the government, in which case many of you might understand the need for moonlighting, I have worked in many emergency rooms, and in fact, have acquired a fair amount of information about pediatrics, but I acquired it the way most pediatricians.

That is, you think you know a good medicine to choose, so you go to the BDR and you try to do your extrapolations and hope that everything works.

I have one other linkage to pediatrics. That is, when I was at the NIH back in 1987, the only guide for the treatment of high blood pressure in children was a report written by a task force 10 years earlier, 1977.

So, I got together a new task force. I can't remember the exact title, but it was something like identification, evaluation and treatment of children with high blood pressure.

It was published in the January 1987 issue of, I believe the journal is called Pediatrics. It is the journal of the American Pediatrics Association, the American Academy of Pediatrics.

You might not be too surprise that, while we had pooled the data for over 170,000 children, we were not in a position where we could say, okay, we have got longitudinal risk data, we know what happens and we have got interventional studies to know how to treat them.