All we could do was take a second approach, which was a normative approach, from the 70,000 children. We could identify what appeared to be normal, and we arbitrarily defined high blood pressure as greater than the 95th percentile. This is corrected for height and weight, et cetera.

For purposes of potential pharmacotherapy, you really have to be in the upper one percentile. Then, when you get to the therapeutics area of the paper, it simply says, well, we really don't have any data, we are flying by the seat of our pants by extrapolation from the adult world.

That, I think, is an example of what we are talking about in all the issues in pediatrics. So, let me get along with my presentation.

I am actually relatively new at PhRMA. I hope that any questions you have for me are not too tough, especially those employing acronyms.

In one of my previous incarnations, as I indicated, I worked at the NIH. You can imagine that, during more than 20 years there, I acquired, I thought, an impressive list of acronyms.

When I first came to PhRMA, apart from verbs and prepositions and articles, I had no idea what people were talking about.

I concluded that, my 20 years at the NIH

notwithstanding, that the only two useful acronyms that would help me in my new job were, first, NIH, the second one I picked up along the way and that is FDA.

I was going to go on to thank everybody, in particular Dr. Murphy, but also Dr. Woodcock and Dr. Lumpkin for inviting me to participate in this meeting.

They obviously are very bright and dedicated to the mission of the FDA. My final question was, and what else? The last reason why I think we should hold them in high esteem because of the many acronyms they have mastered.

First, I will preface my remarks by saying that the comments that I am making are derivative of a statement that Rhonda just passed out, made by PhRMA's pediatric advisory group.

It was too long to present here. So, any comments that I make today are derivative of that. Rhonda has 30 copies. If that is not enough, I have got some extras with me as well.

One of the things I learned today is that, since we wrote those suggestions, not knowing what else would be said today, many of them, it turns out, are going to not be terribly innovative.

If there is one thing I did learn today is, if it is at all possible in future FDA meetings, I would like to ask if I could talk before Dr. Murphy talks, because she has

really addressed a good many of the issues that she raised.

The first issue, then, here is that PhRMA companies are major companies on the U.S. team searching for drugs, especially to get at root causes of diseases, as well as for drugs for intervention and life threatening diseases, and drugs to enhance health-related quality of life.

PhRMA is pleased to have this opportunity to address the pediatric advisory subcommittee, and we are committed to working with this committee today and in the future.

Okay, PhRMA would also like to acknowledge our support for FDA's establishment of a pediatric team headed by Dianne Murphy.

In fact, what we really appreciate is the fact that she has tied together two really -- besides all the pediatric, the pediatric final rule and the pediatric provision in FDAMA which, when you first hear about it, it sounds like it is easy to understand.

As you can tell from today, it is very complicated. So, we are really happy that she has done that.

Not only that, but since our first meeting with her a couple of months ago, our companies are already reporting back to us that the responsiveness of the FDA to their issues related to the pediatric incentive program is

already improving.

PhRMA's companies, PhRMA itself and its companies, have a deep commitment to pediatric drug development. In fact, a just-PhRMA survey of new medicines development for children reports that 109 companies have 207 medicines and vaccines in development for children.

We are really trying to do our part to get going so that, in the end, children can really benefit from that.

Now, what about the identification of therapeutic areas in need of drugs for children.

We believe that this important need would benefit most from a thoughtful team approach. In fact, Dr. Murphy has actually referred to this in several of her points that she made earlier, a team approach to ascertain what really is needed in pediatric drug development.

The team could include, for example, Dr. Murphy's group, this pediatric subcommittee, and representatives from pertinent organizations, such as the American Academy of Pediatrics, the National Institute of Childhood Health and Diseases, and PhRMA.

Okay, this has to do with the ICH. Were the subcommittee members briefed yesterday about the ICH and what that is all about?

DR. MURPHY: There will be more later today, but please, we believe in repetition.

DR. HORAN: Okay, you can see what the acronym stands for. Basically, it is an effort that has been ongoing for about 10 years now, wherein bodies similar to the FDA in the United States, plus the drug companies in the United States, similar in Japan and similar in Europe have decided that, since they all have common goals, why not see if they could integrate their procedures for drug development, drug approval, drug marketing, post-marketing adverse events.

So, the plea we are suggesting is that, since a clearly-identified objective of theirs is to get more going in pediatric medicine, that in your deliberations, where appropriate, that we not forget about them and actually harmonize with them.

This turns out to be a little bit of a thorny issue, but there were already some questions raised. That is, the issues with regard to resolving the problems posed by multi-source products.

As you have heard, if there is a potential for exclusivity, the original manufacturer may very well go after it and obtain the exclusivity.

If it is a drug that is 15 or 20 years old, then at that point not only do we have the innovator company, and not only do we have other companies that are manufacturing this, including the generic companies -- in fact, there are

some good data to suggest that the innovative company, at this point in time, may only be receiving 10 percent of the market share.

If, as a result of the deliberations we talked about, both by this subcommittee and Dr. Murphy's group and other consultants, it is decided, well, this drug really is important, it needs to be done, then the issue arises, well, how can we actually fund this.

So, I am not, here, prepared to give you a solution. It is just one of the many questions, as I think you inferred from Dr. Murphy's comments.

While she and her team have begun to develop approaches for all these things, there are details that are going to need to be dealt with later on.

Cross labeling of me-too drugs, this is thorny and a technical issue and I think it would take too long for me to go into that, but suffice it to say that it is dealt with in the handout.

Okay, we do still have some concerns with FDA's current processing of selected pediatric items. As you have heard already, Dr. Murphy, head of the pediatric team, has already begun to address these issues and, as I said, in some cases to the point where our pharmaceutical companies are already reporting back better results.

So, rather than go into every problem and rehash

things, the problems we have had in the past and the ones we anticipate in the future are in the handout.

We do, as I said, really appreciate the multi-pronged approach and the team approach that Dr. Murphy indicated will be participating.

It is not going to be just FDA or just the subcommittee. There will be opportunities, as appropriate, for experts such as the American Academy of Pediatrics, industry people, to make input, including the National Institute of Childhood Health and Diseases.

In the handout we have listed a number of concerns, which I don't think it would be in our best interests to dwell on. I would point out one or two.

The very first bullet, Dr. Murphy already referred to that as being a priority.

Here is something that we found that could be -- that still may need some attention, but perhaps Dr. Murphy is already working on it.

In our last meeting with her group, we had indicated that there are some scenarios where, in fact, more than one indication for pediatric usage is being sought by a single pharmaceutical company.

We feel it would be beneficial for children, once all the studies have been conducted to satisfy that one indication, that that one indication be approved

immediately, since the other indications may require more extensive studies, or they could be located in other less-efficient review divisions.

Our companies are telling us now that when they submit their interest in trying to get several indications approved, that when they make progress and get one all completed, they are told that the slower division, which is not caught up in its work, they are being told that they still can't release for approval the first indication, because they have to wait until all the conditions are in. In some instances, that could mean expiration of the exclusivity.

I don't know how locked in the FDA is to this, but if it is possible to change that, we feel that would be helpful.

The first one is obvious and the other two, we have certainly touched upon. They are important aspects of what needs to be conducted. You certainly didn't need PhRMA to remind you of that. You have already thought of that yourselves.

This is, I believe, the last slide on PhRMA's concerns. The second and third, I think, are things that we hope will happen.

Again, FDA is to be complimented because, what with PDUFA and everything else, they are earnestly trying to

make more rapid their decisions and get things from point A to point B. We hope that philosophy will also pertain to the last two bullets.

Now, I would like to just finish off my remarks by some educational commentary on clinical trials, which many of you know that such people as Bob Temple, Mack Lumpkin and including Dr. Murphy at the FDA have strongly advocated for years and, indeed, with methodologic rigor.

For those of you in the audience who are already clinical trials aficionados, none of this will be new to you. I ask simply that you bear with me during my last few slides.

I forgot this one. Again, we were not knowing, at the time we were writing these comments, what was going on, and knowing that the FDA had written a very helpful guidance, when it came time to explain to industry and to its own regulatory divisions, how best to proceed with interpreting the law.

They wrote a guidance and it did, we feel, help very much. We certainly expected that the FDA would, in fact, be issuing a guidance with regard to the final rule and especially how it interacts with FDAMA implementation.

I think we have already heard today that that is going to occur and, in fact, it may already be in the works.

So, getting back to my clinical trials, this is

just simply -- I keep forgetting which are my last slides -- this is just simply a commercial and, as Dr. Murphy read to you, a pharmaceutical industry representative is expected to be on this committee. Both today and in the future, we hope to be as helpful as possible.

When I was growing up in academia, and didn't have much to do with the FDA, I was always under the impression that FDA and industry are these two huge gorillas that were always fighting with one another.

In the past few years, I have been really impressed. The areas in which they come together and work well, to me, are far more outstanding than the areas over which they tend to disagree.

So, we, as part of that spirit, do wish to not only contribute to today's meeting, but to participate in the future.

Okay, finally got to clinical trials. As you know, about 40 years ago, people didn't even do randomized clinical trials.

Now, we have come to understand their potency. Methodologically speaking, they are probably the most powerful tools in helping us to learn things about interventions.

Now, in this particular case, the intervention is usually a drug and the placebo is a compound that has been

made up to look exactly like the intervention compound.

Of course, the randomization, half the subjects get the active drug and half get the placebo.

Single blind is one wherein the patient really doesn't know, but the investigator does know.

Then there are also double blind trials, and that is a situation where, in order to make more of an effort at preventing bias, not only is the patient unaware of whether he or she is getting the active drug or the placebo, but the investigator doesn't know either.

Then there are triple blind studies, where, in addition to the patient and the investigator not knowing, also, whatever you want to call it, the safety review board, the DSMV, drug safety review board -- that is a board that is set up to make sure that the trial, if it is getting in trouble, will be stopped if necessary, or if there are protocol violations, et cetera.

They are a neutral third party with no financial interest or anything in it, so, they are keeping everybody honest.

There are some trials in which they are blinded to the results. It is true that, on a periodic basis, they are given outcomes, but they are not told which outcomes pertain to the experimental group and which to the non-experimental group.

Then, there is a rarely used design called a quadruple blind study. In the quadruple blind study, not only do the other three people not know, but not even God knows who got the active drug.

At any rate, that concludes my remarks. I would be happy to answer any questions. If we don't have time, I understand, but I will be around the whole day.

DR. MURPHY: Dr. Horan, before you leave, just because I know that everybody here might not be quite as familiar with all the nuances as I know you are, I just wanted to address one issue on one of the slides.

As you noted, we are working to improve our ability to address some of the issues, but I think that the question you were trying to address is, in addressing the whole active moiety, and one division is able to come up with the studies that need to be done and the other division hasn't, could we issue a partial written request.

That is an issue we are looking at right now. It is the written request that isn't being issued. But we wouldn't hold up the approval.

If a drug was in, if an application was in for approval, that is a different process. I just wanted to clarify for everybody, I think the issue was getting the written request out so the sponsor could begin its studies. That, I think, has been a real concern.

DR. HORAN: Okay, maybe I didn't make myself clear or maybe I did and I was wrong. We have heard from our companies instances wherein they have a particular drug that they have put on the market, and let's say it is for adults.

It already has approval for several indications. Now, because they are aware of the pediatric exclusivity period, they now decide that they would like, since it appears to be appropriate, to get pediatric exclusivity for three indications, the same three indications they have for adults, but now for children.

So, they supply a plan to the FDA, and you go over it. It looks as though one of these indications will probably be able to be completed fairly quickly, because there are very few studies to be done and it is pretty much a slam dunk.

Our companies have been telling us that, under circumstances like those, that when the one indication is final and ready, they are asking, okay, can we have the exclusivity approved, because there are reasons -- some of which we know, some of which we don't know, that the other indications are taking a longer time to process.

Is it possible that they could get the exclusivity extension for that one indication, while still working as hard as they can, and the FDA is working as hard as it can, on obtaining the data that is necessary for the other two

indications.

DR. MURPHY: That is the tension between the implementation of a process where exclusivity dates are expiring and the need to issue a written request that covers all the needs. That is the tension that you are talking about.

As of right now, what we are trying to do is balance -- we are not asking for every possible piece of information that might be applicable, because we can always ask more questions, as everyone knows.

But what are the studies that we really do need. Sometimes it may work, sometimes it may not work. In other words, we cannot just arbitrarily say, well, we are going to issue a written request only for these studies, because that product's exclusivity is going to expire.

That is our tension here in trying to make sure that we balance what we think is really needed, and that we are going to get the information.

I think that is one of the pragmatics of life that we have to deal with. If we ask for such a huge amount of work that there is no carrot at the end of the line, none of it may get done.

There is this tension that we are trying to deal with as we go through this process. So, you were talking about -- it does end up in who might get approval and who

might not get approval.

It is the issuance of that written request that is really the sticking point as to what we put in it.

DR. HORAN: I guess what you are saying is -- maybe this is my misunderstanding is that, if it is close to the time when the drug will run off patent altogether, then even if you were to say -- you really cannot say, you can have six month extended exclusivity just for this one indication that we approved.

I think you are saying, whatever indications you sought, they need to be approved all at once, because it is the drug itself that gets extended for six months, rather than a drug for a single indication; is that correct?

DR. MURPHY: The exclusivity does apply to the whole active moiety for all the indications; you are correct.

The balance here is making sure that we get what we think should be covered, at the same time not creating a situation where you don't get any information.

DR. HORAN: Okay, thank you.

DR. CHESNEY: Thank you very much, Dr. Horan, and also thanks to PhRMA for the very thoughtful statement they have given to all of us.

Our next speaker is Mr. Dave Grinder, from the pediatric pharmacy advocacy group.

AGENDA ITEM: Pediatric Health Information System.

MR. GRINDER: My name is Dave Grinder. I am currently the director of pharmacy at All Children's Hospital in St. Petersburg, Florida.

I am sorry, I may be a little ill prepared today because I have been very busy at work. Work has become overwhelming and I am this close to losing my job, and I am this close to quitting. It has gotten overwhelming.

I have 10 pharmacists on my staff responsible for dispensing medications throughout the day, another three clinical pharmacists, two night pharmacists, to do various functions.

Out of those 10 pharmacists, I am down to five. I have to close our outpatient pharmacy to support the inpatient pharmacy services. That is creating a lot of stress, obviously.

I tell this story because it is relevant to the issues today. As I sat on the plane after work yesterday, thinking about the very primal problem that I have at work, it is very much related to the issue that we are dealing with today.

Pediatrics, every aspect of pediatrics is different from adult pediatric practice, and it is just as true in pharmacy as it is in medicine and in industry.

The dispensing process in the adult institution or

in the adult world or adult practice, is basically to receive a medication order, screen that order for drug interactions, allergies, appropriateness of indication, dose, label it via manually or via computer and dispense it.

In the adult institutions, it is very easy because commercially available products are oriented to this market.

Labeling the product becomes a very easy task. It is a matter of taking it off the shelf, putting a label on it and dispensing it to the nursing unit for administration to patients.

In the pediatric world, it is much different. This is where my problem lies. We receive the medication order, we do the interaction and the allergy screening. We also have to make sure that the dose that is being prescribed is correct, a much easier task in the adult world.

If it is one tablet, it is pretty close to the right dose. In the pediatric world, it is never one tablet. It is seven milligrams, and you may have a 50-milligram tablet on the shelf.

So, we are confronted with, one, making sure that what is prescribed is correct -- and I will come back to this slide.

We looked at the process of screening medication orders for appropriateness of dose. Over a three-month

period, we reviewed 69,000 medication orders, and found 80 in that three-month period to be outside dosing guidelines established by our pharmacy and therapeutics committee.

Sixty percent were too high, 40 percent were too low. Of those 80, 69 were considered clinically significant, and three of those 80 varied greater than 100-fold from recommended dosages.

Now, 80 out of 69,000 doesn't seem like very much, but basically, this is one a day over a three-month period where we have to make significant changes in the doses that were prescribed.

We are committed to review each order for its appropriateness of dose, and it puts a lot of stress, a lot of time on the pharmacy staff.

Once the dose is verified as being appropriate, many times we have to compound the product, because that seven milligram dose is only available in a 50-milligram tablet.

As you well know, we are led blindly into the world of compounding, relying on published literature for extemporaneous stability, bioavailability, et cetera.

The bioavailability literature is poor with extant compounds, but there is some stability data out there that we rely on heavily.

Basically, when we receive an order -- and we

receive, on average, 69,000 over a three-month period -- it is the first time, essentially, that we are using a drug in that size patient.

Granted, we do gather a lot of experience and the first-time effect seems to diminish, but so often we have to invent ways to do things every day. Compounding and lack of product availability slow us down and create a tremendous work load as well.

It is a work load that is pushing me from both ends of the hospital. I have five out of 10 vacancies. Human resources are telling me that I can't manage people. The chief operating officer says, if you can run it with five, then maybe that is all you do need.

If we look at what other hospitals are doing, there is an organization called The Child Health Corporation of America, a consortium of now 38 free-standing children's hospitals, the American Society of Health Systems Pharmacists and the Pediatric Pharmacy Advocacy Group.

They have gathered FTE-type analysis for comparative data. This is, for the next few slides, where some of that data comes from.

We did some time/motion studies looking at how long it takes to prepare an extemporaneous oral liquid. That is basically defined as creating an oral liquid dosage form from a non-oral product and packaging it into a unit of

use package.

It takes, in the hospital, on average, about two minutes per dose to prepare such a thing. That doesn't seem like that long. It really adds up.

In the 35 childrens hospitals that participated in this data base in 1996, we found that there were 10,363 compounded oral doses per month per hospital, which equates, at two minutes per dose, as 11 hours, 20 minutes per day compounding products that are not commercially available.

The financial impact, based on 1999 wages, applying the two minutes, in a more sophisticated study in the ambulatory arena as well as the inpatient arena, the labor cost to develop one outpatient extemp formulation is $3.47 per prescription, on the inpatient side, it is $.32 a dose.

Supplies for an outpatient pharmacy extemp preparation is $4.25. On the inpatient side, it averages to about $.30 a dose.

So, the cost in labor and supplies to dispense one extemporaneous prescription in the drug store is $7.72, on average.

That doesn't seem like much, but in Florida, Medicaid reimburses the cost of the drug, plus a $4.23 dispensing fee.

So, any pharmacy that fills an extemporaneous

compound in the community, and it is a Medicaid patient -- and in our institution, in the outpatient pharmacy, 60 percent of our patients, are Medicaid. We are losing money.

In terms of time that we spend expending extemporaneously prepared oral liquids, it is about nine percent of our time in the institution. What impact does that have.

Well, it takes a lot of people to get this much work done. In a typical adult community hospital, they can run a pharmacy with fewer people.

I am being crunched from the COO, who has come from the adult world, to get into the number of two to four FTEs per 10,000 patient days, where the pediatric hospitals that I referred to earlier are averaging seven pharmacy FTEs per 10,000 patient days.

I have tried the best I can to get as close to four as I could, but it has created stress within the staff and resignations are pouring in. It is a difficult situation.

It is a difficult situation that leads to an increased risk for medication errors. At the December 1997 symposium on medication errors sponsored by the Pediatric Pharmacy Advocacy Group in cooperation with the Institute for Safe Medication Practices, we identified issues that increase the chance of medication errors in pediatrics.

Certainly, the significant maturational changes that we see from the premature neonate to the adolescent account for some of the errors that we see, the dose based on weight that I referred to earlier, the lack of available dosage forms.

It has been shown that 20 percent of medication errors in pediatric are related to oral liquid medications. Drug delivery challenges and lack of use information, the medication error literature is full of recommendations for reducing medication errors. That is to make everyone aware of how to use that drug, or we are stuck, as you are well aware. We don't know how to use these drugs initially, or even with time and experience.

So, our medication error rates in childrens hospitals are higher than in the adult world, and you can understand why.

In addition, there are parent and patient concerns with extemporaneous formulations. I mentioned that it costs pharmacies to dispense extemporaneous compounds. Well, if they knew that -- and many of them do -- they are going to refuse to do it.

How many pediatricians here have come to them and said, I can't find anyone to fill this prescription. Is there anything else you can give me.

I can tell you, in my environment, I see it every

day. When they do find a pharmacist willing to compound something, the instructions, the methods vary from pharmacy to pharmacy.

Just this week, we had a patient admitted to the hospital with uncontrolled hypertension because the pharmacy that filled their captopril solution used a 50/50 mixture of orasweet and oraplus, which is a flavoring agent and a suspending agent.

The literature shows that stability outside of an environment with ascorbic acid is a matter of hours. We found that 10 milligrams of ascorbic acid per ml will allow stability of captopril for up to 30 days, and that is what we use. But not everybody knows that.

Certainly, the CVS pharmacy on the corner in Silver Spring is probably unaware of that. Yet, if they are confronted with filling a captopril solution, they will use whatever they think is appropriate.

So, we use data bases to try to justify our existence, improvement in patient therapy. The Pediatric Health Information System is such a data base.

The Pediatric Health Information System is a data base originated by the Child Health Corporation of America and managed by HCIA. That acronym is beyond me. They are in Michigan. There are 28 participating children's hospitals.

The way the system works is that the patient bill is electronically submitted to the data base clearinghouse in Michigan. Line item charges are identified for each patient at each institution and thrown into a big bucket, for the purpose of developing some comparative utilization analysis within the hospitals.

What it is turning into is that, if you just throw them all into a big bucket, you can see utilization in pediatrics throughout the country.

There are sophisticated measures built into the system to guarantee that the data is as accurate as can be, unlike the current prescription monitoring system in place in this country, where data from electronic billing submissions are scanned to give us prescription volume reports.

The PHIS data base does not rely on the national drug code. In the retail setting, the national drug code drives utilization figures.

The problem with captopril solutions and all the other extemporaneous compounds that we have found in the PHIS data base, is that there is no NDC associated with captopril solution. There isn't a commercially available product.

In the retail setting, that current system cannot capture captopril suspension or solution utilization, unless

the pharmacist simply charges for captopril tablets, in which case you will identify a prescription for captopril tablets.

The PHIS data base recognizes this and has rules built into the pathway that, regardless of what the children's hospital calls a particular product, it is mapped to one entity in the data base.

So, the captopril or capatin suspension or solution or liquid or oral liquid all means the same thing. It is not NDC driven, so the numbers we get are fairly accurate.

These are some of the things that come off that data base as items that we compound. Just for example, captopril solution, in 1997, there were 2,654 patients within these, at that time, 21 children's hospitals who received captopril solutions.

Right now, there are 28 participating hospitals, who account for about 20 percent of all the pediatricians in the country, meaning 20 percent of the pediatricians have admitting privileges at these 28 children's hospitals.

The problem is, these data are inpatient driven only and, with all of these products, they are usually chronic, less acute in nature, and are given in the retail settings.

So, some extrapolations have to be made to

identify or estimate how often these products are used in the ambulatory setting.

I think it is a reasonable start and certainly a potentially viable tool that this subcommittee should consider as something to investigate to establish the 50,000 number that is currently in place.

Any questions regarding my life or the PHIS data base? I really am a sensitive manager. It is not that they are leaving because I am insensitive. I will prove it by telling one joke.

How many men does it take to open a bottle of beer? The answer is none, because it should already be open when she brings it to you. [Laughter.]

DR. CHESNEY: Thank you very much, Mr. Grinder. You have also articulated the urgency of the issues, not only for children but also some of the issues that many of us are feeling in states that are heavily managed care.

Our last speaker for this morning is Mr. Timothy Westmoreland, who is a public policy representative of the Elizabeth Glaser Pediatric AIDS Foundation.

AGENDA ITEM: Elizabeth Glaser Pediatric AIDS Foundation.

MR. WESTMORELAND: I need to begin with something of a renaissance apology. It was the custom, during the Italian renaissance, for artists bringing their work to

their patrons to say that, nothing that I, humble wretch that I am, could produce for you would be worthy of your attention, great Medici, but would you look at this for me.

I sort of need to do that for this group, because I am really sort of five levels removed from the daily practice of pediatric medicine.

Not only do I not work with children, I don't work with people who work with children. I don't work with people who work with people who work with children. I don't work with people who work with people who work with people who work with children. I work with the lawyers and lobbyists of people who work with people who work with people who work with people who work with people who work with children.

Having said that, I think I can probably say that I know as much about how the Congress arrived at the legislation that produced the FDAMA provisions on pediatric exclusivity, and perhaps as much about the administration's deliberations on the rule as anyone you are likely to find in an advocacy group. That might give you some pause, by the time I finish my discussion here.

Having said that, let me make a few brief remarks on behalf of the Elizabeth Glaser Pediatrics AIDS Foundation, although I am generally going to abbreviate my remarks, because I think most of those have already been

covered by other speakers.

Then, if I could, I would like to extemporize a moment on some of the questions and points that have been raised in this morning's meeting and be a little more directed.

The late Elizabeth Glaser started this foundation to promote and support research and drug access for children with HIV.

As part of that effort, the foundation has been a strong advocate for both the FDA rule being discussed today and for the pediatric exclusivity incentives that were part of the FDAMA law.

I should emphasize the foundation has been advocating not just for children with HIV, but for all sick children.

In the foundation's view, children should not be an afterthought, but too often they have been an afterthought in pharmaceutical development over the past 30 years.

Despite encouragement, streamlining and a range of appeals that have been outlined for you this morning, drug manufacturers were slow to begin voluntarily testing most drugs for children.

The FDA rule and the exclusivity legislation are not only necessarily, but are long overdue. Until these

measures were enacted, it was presumed the drugs would not be tested in children, unless there was a special reason to do so. Even then, the testing may come years after approval of the drug for adults.

The rule and the legislation that are being discussed this morning have reversed that presumption. It should be the presumption now that the drugs will be tested in children unless there is a special reason not to do so, and that the testing will be carried on simultaneously with adult testing, unless there is a special reason not to do so.

This reversal in paradigm, this paradigm shift, I believe, is the most important thing that has been accomplished with all the sound and fury that has accompanied the development of the pediatric exclusivity provisions and with the development of the rule.

Having said that -- those are the prepared remarks. I will submit the other five pages of my statement for the record.

Having said that, I would like to respond to a few of the things that have been raised this morning in the special issues or questions.

The first one, I think, that was mentioned was, is a six-month exclusivity period sufficient. This was a wide debate during the time of the adoption of the FDAMA

legislation, with some pharmaceutical manufacturers actually suggesting that they needed five years of continued exclusivity in order to make the incentive worthwhile.

I would argue for you quite clearly that the six months of exclusivity is plenty sufficient for the development of pediatric studies under this provision.

The Office of Technology Assessment -- may it rest in peace -- decided in the late 1980s, or estimated in the 1980s that one year of continued market exclusivity for an average drug was worth $100 million in extra sales over generic competition.

The six months can be anticipated to be worth $50 million to the average drug.

I would say, now, that first of all, that study is somewhat dated. Many of the drugs that will be before you for your consideration, or before the agency for its consideration, will do much better than the average $50 million.

I would point out, for example, that Prozac enjoys -- the last time I saw the drug listed in the Wall Street Journal -- enjoys a $1.8 billion domestic market. The six months of additional exclusivity against generic competition could be expected to more than amply compensate the brand name drug company for the development of pediatric indications.

I would also point out that spending for pediatric indications can, in most cases, be anticipated to be quite low. It may be as little as $250,000 for a routine safety and pharmacokinetic study.

I do acknowledge that there will be difficulties in formulation for some drugs and there will be difficulties in recruiting and retaining subjects for other drugs.

I would start out by answering the question, is six months enough, yes, the six months is plenty.

Even if you think that my reasoning and my elaboration of the OTA data are not compelling enough, I would suggest that the screen that showed 104 applications to this point is even more compelling than I could ever be in saying that six months is more than sufficient.

The next question that was raised that I would like to give some sort of an answer to is, how would people consider developing incentives for drugs that are generic, and drugs that have lost their patent protection.

I would say that, during the time the Congress was looking at this legislation, the advocates, the Congress and many of the academic experts tried, but couldn't figure out how to do it.

If you have got 10 companies manufacturing the same generic product, it is probably inadequate to suggest that one of them could rush to the FDA's door and get six

months of market exclusivity, keep the other nine companies off the market for a mere period of six months and then come back.

Even the generic trade associations, which are quite interested in some form of incentive for generic drugs as well, finally agreed that this was an inadequate way of doing so.

On the other hand, if you were to extend market exclusivity beyond the six months, there is a question of how long you want to jack up prices for public purchase.

So, if anyone has other ideas, the advocacy community is more than eager to hear this. But we have worked our way through this and can't find anything.

The third thing I would emphasize is that I don't think anyone anticipates that any of these measures -- either the exclusivity provisions or the FDA rule -- will hold up approval for adults.

I can say on behalf of the foundation that we believe that holding up approval of a drug for adults is unethical, that adults have the need to have these products as soon as possible.

Unlike some other interests in this debate, we also would maintain that artificially holding up or postponing the approval of drugs for children is equally unethical.

We would urge the committee to do everything possible to exercise deferrals and waivers very sparingly.

I would also note that the regulation itself does not anticipate actually removing adult approved drugs from the marketplace, even in the face of a continually uncooperative manufacture who does not participate in the development of pediatric drugs.

The regulation calls for a final remedy of seeking injunctive relief from a court to compel the manufacturer to develop these drugs.

If the manufacturer continues to disregard the court order or injunctive relief, to face civil contempt fines.

It does not anticipate -- and indeed, the final rule lays out clearly -- that the FDA is not anticipating withdrawing a drug from the market because of a failure to develop drug indications for children.

In addition to that, some people have discussed this morning the difficulties of recruitment of pediatric patients for trial.

I think that the HIV/AIDS example has something to suggest, not so much to the FDA as it does to the drug companies on how to work together with some of the advocacy groups in this effort.

The Pediatric AIDS Foundation does, indeed,

sponsor research trials, and has also helped to hook together manufacturers who want to conduct pediatric trials with pockets of practitioners who have patients who would benefit from such trials, or who might benefit from the ultimate benefit.

I would also point out to you that title IV of the Ryan White Care Act, which is a program to support clinical care services to cities, states and clinics around the country, Title IV of the Ryan White Care Act is explicitly devoted to recruiting women and children.

The Title is for providing clinical care to women and children, but it explicitly requires these clinics to provide access and coordinated access with ongoing research opportunities.

In the late 1980s, the NIH scientists, in many cases, said they would be more than happy to do pediatric HIV trials, but found it difficult to recruit and retain patients.

In an effort to solve this problem, the Congress put together Title IV of Ryan White, to provide services for those very patients, and then to encourage them to participate, with informed consent, of course, in clinical trials.

I would suggest that not only can you use a model like that, but you can also turn to your other public health

service colleagues, who run community health centers, who run the maternal and child health block grant program and, indeed, who administer Medicaid and other managed care kinds of programs, to try to coordinate efforts to encourage state-of-the-art care in coordination with research trials.

It was also pointed out that the NCI has the PDQ system and that a data base on trials has been productive in that area.

I would point out that another part of the FDAMA legislation required the creation of a clinical trials data base, not only for cancer, and not only for HIV, where it has also been successful, but for all clinical trials.

It was an amendment put forward by Senator Snow and Senator Feinstein, which was adopted overwhelmingly, and it is my understanding that the NIH is in the process of developing a clinical trial data base right now, which will be available not only over the internet, but also available to primary care practitioners.

I was interested to hear the stories of the Inspector General trying to put together some coordinated efforts.

Finally, in response to the harmonization discussion that was recently raised in brief there, I would also note for you recent articles in the European academic press, which have pointed to the EU and the UK -- especially

the UK -- is anticipating trying to do the same model that the United States has now developed, in trying to find some form of exclusivity and trying to find some form of mandate -- the carrot and stick model -- to go together.

I have forgotten the name of the committee -- the Royal Committee of Pediatrics, I believe -- is putting together a data book of current recommendations.

Also, pediatric activists over there, advocates and activists, are advocating the adoption in the EU pharmaceutical system of a system of exclusivity, not unlike that already adopted in the United States.

Having said those things, I want to also suggest that the committee also beware of a few things that have come up along the way.

The first one I would suggest is, beware of something -- and I do not make this word up myself, I promise -- beware of salami slices.

Salami slicing arises from the field of orphan drugs. Orphan drugs, as you may or may not know, grants seven-years of extended exclusivity of a drug for a small population which is judged to be not commercially viable to develop drugs on its own.

That seven year exclusivity is for any condition or disease that has fewer than 200,000 patients in the United States.

We have discovered, in the orphan drug law, that manufacturers have approached the FDA Office of Orphan Products with increasingly narrow indications, so that they can first get under the limbo rod of 200,000, by asking for a very narrow indication.

Secondly -- this is what I am particularly concerned about -- they come back and get another period of exclusivity for the next narrow indication, and then another period of exclusivity for the next narrow indication.

This effectively creates an immortal period of exclusivity, which is, in turn, referred to not as salami slicing, but as evergreening.

I would urge you to be cautious of salami slicing as you look at the narrow indications that were just being discussed.

I think you are correct in saying that you have this tension between trying to get as much information as possible, or killing the goose that laid the golden egg and not getting any information at all.

I do think you should be rigorous in looking for artificial distinctions between requests for extended exclusivity.

I would point out that the legislation, because the Congress is more than aware of salami slicing and evergreening going on in the Orphan Drug Act, provides for

only one period of extended exclusivity under the FDAMA legislation for pediatric indications.

I would caution you that, with the five-year sunset rapidly approaching, that it is not beyond my imagination that salami slicing could occur, and thus, hold children in the next narrow indication hostage to a proposal to amend the law to allow, not a second evergreening, but a third evergreening or fourth evergreening, because there will always be desperate parents and desperate children on the other end of that narrow indication. So, I would urge you to be particularly cautious about that.

I would also urge you to be cautious of data being withheld on purpose. This comes from the rule of unintended consequences.

By rewarding companies that previously had not responded to the need for pediatric data, we have created a system that may, indeed, inadvertently encourage companies to withhold pediatric data until they are promised exclusivity.

I think some of this is perhaps -- I don't want to judge too quickly -- visible by companies waiting for their letters before starting their pediatric research activities.

I would argue that companies waiting for letters from the FDA before starting research activities is, first, at least partially avoidable.

You have heard today that user fees are not available for this purpose, that extended pediatric indications does not come with user fees to help the agency finance the extreme labor intensive work of the agency in doing this.

I am hoping to put together, recreate the same happy union between pharmaceutical companies and pediatric advocates that created the pediatric exclusivity, now to go to the appropriations committees in the House and Senate and ask for funding to try to make it possible for the agency to do pediatric exclusivity with new money, not robbing Peter to pay Paul, but with new money to hire staff to be able to work on this area.

Secondly, I would say that holding data until the letter of request is received is unnecessary. Study design and study development and studies themselves can begin long before the FDA puts together a final design, and can be altered as the FDA comes up with its final negotiated letter of agreement about how the study should be put together.

Finally, I would say that deliberating delaying studies is unethical. Companies who wait until they receive their pediatric request, when they know full well that they could begin their pediatric studies, are in some fashion waiting to be paid until studying children.

This is quite different than the argument that

these studies are either unethical or impossible or highly impractical, the arguments that the companies made about the FDA rule to begin with.

If everybody understands that these studies can be done, but we are only waiting for the FDA letter to guarantee six months of additional exclusivity, I think this is the unintended consequence of rewarding companies for the development of pediatric extensions.

Finally, I would say that I would urge you to use waivers and deferrals quite sparingly. A small patient population should be accepted as an excuse for not doing research only when all reasonable efforts to recruit pediatric patients have failed. This is not a judgement that should be undertaken lightly.

I would go even further and argue that no group of sick children is too small to command research on drugs that are believed to be effective in adults.

The license to introduce drugs into the American market and, thus, into the world markets is worth a great deal to pharmaceutical companies.

It is not too much for the nation to ask that drug companies return the favor, by looking out for the interests of the youngest patients in America.

Others have, in this same line, argued that the rule itself is too costly. I find this a disturbing

argument.

The response should simply be, too costly for what, healing sick children? Surely this cannot be the intended meaning of the argument, but if the argument is that pediatric is too costly for pharmaceutical manufacturers in the current environment to bear, it is not a credible argument.

The FDA has estimated that the maximum cost to be incurred from its rule is about $20 million annually. I think by any reckoning, the number of sick children who stay sick, who have unstudied side effects and adverse reactions, the numbers of needless hospitalizations, or the eight ten/thousandths of one percent of the revenues of only the top 10 pharmaceutical companies in this country amount to a very extremely small cost for this result.

Finally, I would say, in thinking about this, that you should, as I have to, as others in this room have to, beware of the potential of a PhRMA lawsuit.

I was delighted not to hear this mentioned this morning, but it has been a widespread, worst-kept secret in town, that PhRMA is considering a lawsuit, or has considered a lawsuit, to invalidate the FDA rule, arguing that there is no authority for it to be done.

I am delighted that this seems not to be the current PhRMA pursuit, but I would encourage you to keep in

mind that exclusivity is the carrot and the FDA rule is the stick, and only with the one-two remedy are we certain that we are going to be able to get the advances in pediatric medicine that children deserve.

In closing, let me return to the reasons that this meeting is occurring. From the early elixirs to the recent AIDS drugs, the problem with the exclusion of children from research has never been adequately solved.

This rule and this incentive take a giant step toward that solution.

The Pediatric AIDS Foundation thanks you for the opportunity to take part in your meeting, and we promise our full support as you move forward. Thank you very much.

[Applause.]

DR. CHESNEY: Thank you very much for that very eloquent and feeling commentary.

I understand we don't have anyone registered to speak in our open public hearing. Is there anybody who hasn't registered who would like to speak?

If not, I think we will end this session for lunch, and restart the next session at 1:30. Thank you.

[Whereupon, at 12:13 p.m., the meeting was recessed, to reconvene at 1:30 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:37 p.m.)

DR. CHESNEY: We are ready to get started. Our first speaker will be Leanne Cusumano, who is on the regulatory policy staff at the Center for Drug Evaluation and Research. She is going to speak to us about the famous priority list.

AGENDA ITEM: Priority List.

MS. CUSUMANO: Hi, I am Leanne Cusumano. I am in CDER regulatory policy. I am here today, as we just said, to talk about the list of drugs for which additional pediatric information may produce health benefits in the pediatric population. That is why we call it the list, because it is a heck of a lot easier.

We have got three goals today. The first goal is to understand the process that FDA used for developing the list.

The second goal is to understand what is included on the list. The third is to understand how we use the list.

There have been a lot of issues, a lot of discussion, a lot of misunderstandings, unfortunately, about this. So, hopefully we will clear all that up today.

Why does FDA even have such a list. We are not really an agency who is charged with determining what medicines are most important. We are really an agency that

approves drugs.

Well, we have got a list because Congress told us to make a list. This mandate is embodied in law, the law is pediatric exclusivity.

It is part of the modernization act, which was enacted on November 21, 1997. It required publication, by May 20, 1998.

Also, for lawyer types I always like to include these things, the United States Code site is 355a(b), or you often hear it referred to as section 505A(b) of the Act.

Section 505A(b) directs FDA to consult with experts in pediatric research to develop, prioritize and publish the list.

Who are experts in pediatric research? Happily, Congress gave us a little bit of guidance. The legislative history for the act tells us, tells FDA, you are to consult with the following experts in pediatric research: AAP, The American Academy of Pediatric, NIH, National Institutes of Health, PPRU, which are the Pediatric Pharmacology Research Units; and USP, United States Pharmacopoeia.

In addition, we said to ourselves, we would like to talk to some other people, the people who develop drugs. So, on this side, we also talked to the generic trade associations and to PhRMA.

All right, how did we develop this list? First,

we sat in our office and said, where do we have a list of drugs.

We have a list of drugs in the orange book. The orange book is FDA's list of approved drug products. So, we started with that list. If you want to look at it or do searches in it, we have got it on our web site.

Then we took the orange book to our review divisions and said, look at these drugs, tell us the ones that you think need pediatric study.

We also met with those experts that we talked about earlier, and then, on March 16, 1998, we published a draft version of the list.

As a result of that comment, we got comments. We got about 89 comments from outside people, people like pediatric researchers, professors, people who were interest in pediatric research.

They told us things like, this drug shouldn't be on the list, or that drug should be on the list, of you should use some different criteria.

We took those comments and we went back to our divisions and said, well, what do you think. Should these drugs be on the list or shouldn't they.

Then, based on all of that information, we published the list on May 20, 1998, and now we are in the process of updating the list, because that is required under

the statute, too.

How many drugs are we talking about? Well, in the orange book, there are a whole lot of drugs, as you can see.

The orange book distinguishes products between NDAs and drug products. NDAs are smaller, because multiple products can be included in one NDA.

So, you are talking about almost 10,000 prescription drug products, and then about 300 over-the-counter products. That is how many are in the orange book.

How many drugs in the orange book -- the real question is, because pediatric exclusivity will only provide incentive for drugs that have existing patent life for exclusivity, how many of those 10,000 drugs have existing patent or exclusivity protection? Only about 500.

So, we published the list on May 20, 1998. We announced the publication in the Federal Register. We put it up on our web site -- that is the site right there.

It is available in the public docket under that docket, and it has to be updated at least annually.

So, now you know how we published the list. What is this list?

The list is a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population, and we are going to talk about what each of those things are.

The first and most important point, which I can't tell you how many times we have had questions about, what is an approved drug for the purposes of the list.

It is an approved, active moiety for an approved indication that occurs in at least part of the pediatric population.

So, let's take the example of -- I often hear like prostate cancer. Prostate cancer does not occur in the same way, or perhaps not at all, in the same way -- ovarian cancer is another one -- as it does in the pediatric population. It is a different disease.

If you have got a drug approved for prostate cancer, it is not going to be on the list, if that is the only indication it is approved for.

What is an active moiety? I think of it in layman's terms. An active moiety is the part of the drug that makes the drug works the way it does.

I also include in here this big long text, which is our regulatory definition of active moiety. It is in our regulations at 21 CFR 314.108.

I am told, often, when I talk to scientists or medical officers, that this definition of active moiety is slightly different from what most scientists think of as an active moiety. So, it is there, in case it comes up.

The important point about active moiety is that

many different drug products can be marketed with the same active moiety. That is important for the pediatric exclusivity provisions that were talked about earlier.

Pediatric exclusivity attaches to every drug product that the sponsor has containing the active moiety. That is why this definition of approved drug is so important.

What does the list look like? Basically, there are three big parts to the list. There is the introduction, there is the priority section of the list, and then there is the rest of the list, that often gets lost in the haze.

That is approved drugs as we define them for purposes of the list, an approved active moiety for an approved indication that occurs in at least part of the pediatric population, and it is in the orange book. In other words, it is approved.

Those are the three parts of the list. A lot of people -- and we will see why in a moment -- get caught up on the priority section of the list, and kind of forget that the overall list is everything in the orange book that is an active moiety for an approved active moiety for an approved indication that occurs in at least part of the pediatric population.

This is the introduction. This is what it looks like. It is the first five pages of the list. The

introduction has some good descriptive background, which is basically what I am talking to you about here today.

There is background, there is the process, there is the content of the list, criteria for inclusion of the drug in the priority section of the list -- which we are going to talk about -- format of the priority section, requesting updates, telling people, please tell us if there are additions to the priority section of the list. It tells you how we published it, and I think that is it.

So, what is this great priority section of the list which everybody hears about. To be on the priority section of the list, not only do you have to be an approved active moiety for an approved indication that occurs in at least part of the pediatric population, you have to meet one of three criteria.

The first criteria is, you must be a significant improved compared to marketed products. So, Dr. Murphy always says to me, drugs for the treatment of HIV, let's say you have got one that has a significantly better safety profile. You know, you have got kids taking it and they are not throwing up all over the place.

That is a significant improvement compared to marketed products, or it could be. That drug would make the priority section of the list.

Second, or the drug must be widely used as

measured by at least 50,000 prescription mentions per year. Generally what we are talking about is IMS data. Or, additional therapeutic or diagnostic options are needed.

Sometimes you have got first line therapies out there that not everyone is responsive to. You need some second-line therapies. Those kinds of drugs would fit into this category.

What does the priority section of the list look like? There are two attachments. Attachment A lists the drugs regulated by the Center for Drug Evaluation and Research, and attachment B lists the drugs regulated by the Center for Biologics Evaluation and Research.

How many drugs are we talking about? We are talking about 450 drugs regulated by CDER and about 25 regulated by CBER.

The good thing about biologics is that a lot of those drugs -- you know, you are talking about vaccines -- those drugs are developed for use in kids. So, a lot of those are labeled, but there are still some gaps.

When you look for a drug on the priority section of the list, how do you find it? Well, the priority section of the list is arranged by therapeutic class, which basically, to us, means according to the division where it is reviewed. Within therapeutic class, it is in alphabetical order by active moiety.

The important part about this is, because the same active moiety could be regulated by multiple divisions, the same active moiety may be on the priority section of the list in multiple places.

Finally, there is an N column right now that indicates ages where there are gaps in the labeling.

This kind of gives you an overview what our review divisions are. The first part are all drug review divisions.

I have specifically indicated the biologics, therapeutics, bloods and vaccines, if you are looking for something in particular. These are listed in the order that they are listed on the list.

What is the difference between this priority section and the rest of the list? Well, the first difference is that when somebody sends a proposed pediatric study request to FDA saying, we want a written request, here are the studies we want to do, we process those proposals first. We look at them first.

Why? Based on those three criteria that we talked about, those are the drugs that we believe it is probably more important to get labeled first.

This is the big area of confusion. There are lots of things that being on the list does not mean. It does not necessarily mean that the drug is eligible for pediatric

exclusivity; in other words, that the drug has any remaining patent or exclusivity life to which pediatric exclusivity could attach.

That is not necessarily true. If you look on that list, there are lots of antibiotics on that list that need pediatric labeling.

Antibiotics that weren't approved under section 505(b), the old antibiotics aren't eligible for Hatch-Waxmann or exclusivity, so they might not necessarily be eligible for pediatric exclusivity.

They are still on there. The list doesn't require that they be eligible for pediatric exclusivity to be included.

It does not mean that the drug has received a written request. We are very specific in our guidance document in saying that, a written request is a specific document that is signed by the office director.

To give you an idea what that is going to look like, this list is not a written request. It also does not necessarily mean that new studies have to be undertaken to fill the gaps in the labeling for pediatric uses.

This issue came up earlier where we were talking about literature. There might be researchers out there who have already done the research that needs to be done to fill the gaps in the labeling.

Basically, what we are saying is, we opened up the PDR or looked at the most recent labeling that we have on file for your product, and we know that this drug is used in the age groups, let's say, two to 16. Yet, you have in your label a statement that says, pediatric use has not been proven safe and effective below the age of eight.

Well, there is a gap between two and eight. Maybe you have got studies in your IND. Maybe there is literature out there that will fill that gap. Don't know. You have got to come talk to us.

It also does not mean -- which Dianne emphasized and Rosemary emphasized -- that a sponsor is required to take any action.

This is kind of the weak side of pediatric exclusivity. There is no requirement that anybody do anything.

So, now it is almost a year later. It is almost May 20, 1999. We are required under the statute to update the list at least annually. How are we going to do that.

Well, one of the ways obviously is, as new active moieties get approved from year to year, the question is, like that chart that we have shown earlier, we approve 40 active moieties a year. Twenty-five have application in the pediatric population. Those all would get added to the list.

New indications, you have got an already approved active moiety. You get a supplement for a new indication. That supplement gets approved. You only have adult data. If the indication occurs in the pediatric population, that goes on the list.

Unfortunately, we are not perfect, as we have discovered in a lot of ways as we have worked through this process with sponsors and companies coming to us and saying, well, this indication is on the list and that indication is not on the list.

We are trying our best to go back and look at the list, make corrections based on reconsideration or errors, and trying to get the list into good shape.

Finally, what we have told people is, if there are particular drugs that you want to see added or removed from the list, send us a citizen petition. We will review it in a timely manner and either make the change or explain why we are not making the change.

We have kind of been talking about this along the way, but what issues has FDA had to clarify as we have gone along.

Like I said, the definition of approved drug. The reason FDA has had to clarify this is because it is a little bit different from what we talked about in other sections of the statute, but this definition is what makes sense in this

part of the statute.

Approved drug equals approved active moiety plus approved indication that occurs in all or part of the pediatric population.

Whether additional studies are necessary. What we definitely do not want sponsors to do is go out and start doing studies without even talking to us to see if those studies are really necessary.

There have been a lot of issues and it is something that we anticipate taking to the advisory committee, about extrapolation from adult indications. Really, the sponsor should come and talk to us.

Age groups have been, unfortunately, a major issue for us, primarily because the age groups on the list are kind of artificial.

They are broken down into neonates, infants, children and adolescents. That is not necessarily the way drugs work.

There may be physiological or developmental differences that make you want to study the drug in different age groups. So, we have had issues with the age groups.

Indications, sometimes indications don't make the priority section of the list. But they should be on there, or they are on the priority section of the list and maybe

they shouldn't be. What is the solution?

The solution is for people to come and talk to us, please. I know we have had complaints that we have been a little slow on the uptake.

Some of it is because there have been complex scientific issues. In a lot of cases, we are getting -- I mean, if you are talking about an antidepressant, the type of study that we are going to need for that antidepressant is going to probably be the same across the class, probably.

So, come and talk to us because hopefully we are ironing out those issues and being able to process things a little faster.

Okay, what issues related to the list do we anticipate taking to you? First, whether a drug belongs on the priority section of the list. Does it meet one of those three criteria? Are the criteria we are using good criteria?

Second, as I was just talking about, is the disease course the same in children as it is in adults. This is something that, in some fields, there is not a lot of scientific certainty about. It is something we need advice on.

Okay, so, what have we covered? First, approved drug equals active moiety, approved active moiety plus approved indication.

We have got the priorities, significant improvement, wide use, meaningful therapeutic benefit.

The idea is that the list doesn't necessarily tell you what studies are necessary, just that there are gaps in the labeling.

Finally, pediatric exclusivity doesn't require anybody to get anything.

You can get additional information on our web site. Believe it or not, we are a very web oriented agency, which can be tough for people who aren't necessarily, but there is a lot of information on our web site, not only about the list, but about pediatric exclusivity and the pediatric rule.

Then we have the easy-to-remember -- the phone will be ringing off the hook, I am sure, but at least they would be a starting point to be able to direct you to somebody -- pediatric staff, 301-594-PEDS.

Okay, one of the things that we are thinking about doing -- and I wanted to take the time to ask the advisory committee if they have any thoughts about it -- is in updating the list, we are thinking about taking the ages off the list.

We have had a lot of issues with it, and we are not sure how relevant they are for people looking at the list, or how helpful, if they are more misleading than not.

I didn't know if anybody had any comments about that, or about anything else that I have talked about.

DR. CHESNEY: Thank you very much. That was very, very clear. We appreciate that. Any comments from the subcommittee, specifically in answer to her question about whether the drugs should be listed by age.

DR. FINK: It would seem like, at least for some of the drugs that are listed there, the gaps are in a specific age range, like zero to two, and not through the whole pediatric age range. To take that off the list would create unnecessary questions.

DR. MURPHY: From the prior slide that we had shown the committee, I guess what we are saying is that we are finding that many of the studies that we are requesting do not fit into these arbitrary categories, because either the disease occurs in a different way or the question you are trying to answer is for a specific reason having to do with absorption, metabolism, whatever.

We found people were confused, when they looked on the list and it said, you had to have studies between two months and two years.

Really, the question they were asking was limited to just the lower end of it or just the higher end and into the next age category. So, they weren't sure whether they should ask for both categories, or just what they felt was

important.

We are asking you just to comment, having now lived with this for 48 hours and thinking about it more than that, hopefully, if you got to look at this list, if you had any immediate impressions as to whether you thought this was useful in defining where the gaps are, or we should list just the product or the moiety or the indication and then people would come in and say, this is where we think the studies should be done.

If you don't have any comments, that is fine, but that is sort of how we are phrasing the question.

DR. EDWARDS: I thought it was helpful to know what data did exist. I thought when you said no, that you didn't need information, that there was information there, and that was very helpful.

So, one possibility would be to say age groups in which information does exist. I think that would be the lowest common denominator, making sure you had that. I am not so sure I know how to answer the other part of the question.

DR. GORMAN: A question for clarification from FDA. Is the agency required to link the -- assuming that our goal here is to get appropriate labeling for pediatric practitioners -- is the agency limited in labeling to just those age divisions, or can they choose, in the label to put

in the data that is available.

So, if a company comes in with a three to 16 age range in which the study is performed and shown to meet the criteria to get labeling, will the FDA have the ability to label products in that manner.

DR. CUSUMANO: Sure, there is absolutely no reason FDA can't label products, and in fact, they do that now.

In fact, I heard from divisions, you know, the study was done down to six. We know the disease isn't any different down to four. We are willing to say labeling down to four. FDA definitely has the flexibility to use the data that is given.

DR. CHESNEY: I have seen this list several times through the academy. I have found the ages very confusing. You don't know the quality of the data that is available.

I guess my preference would be to do what Dianne suggested, which is not to list the ages, but let the companies come to you to find out what is needed and what the quality of the available data is.

Any other questions on anything about the list?

DR. EDWARDS: I think the multiple drugs that are for the same indications are very confusing to me. I don't know, for instance, whether if you have three me-too drugs, that if one does studies, then the other two will get labeled, or whether a marketing division can say, well, we

are the only drug of these three me-too drugs, that has data, and you should bias for that reason.

MR. CUSUMANO: It is kind of interesting because we had this issue with the antihypertensives. You might notice that there is quite a number of antihypertensives on the list, for example.

The thing is, all of those are on the list because additional therapeutic options are needed. Maybe that might be an issue that comes here, the first however many are labeled for use in pediatric populations, then maybe the rest might very well come off the priority section of the list.

Would one get labeled based on the others? Not unless they had a right of reference to the data, no.

DR. LUBAN: Are you planning to do multiple lists and potentially have them by disease category as well? Clearly, there are some diseases that simply don't exist in certain age ranges, where it would be futile to even consider doing the clinical trials.

MS. CUSUMANO: There are really two issues here. One is the list for pediatric exclusivity and the other is the field of waivers for the pediatric rule where we do talk about not only drugs but disease states.

You are required to do certain studies under the pediatric rule, whereas the pediatric exclusivity is

optional.

We publish a list of 20 -- they were all disease states, I believe. Dr. Roberts is going to talk about this a little bit more.

Will we have multiple lists? I guess the true answer is yes, but the purpose of one list will be pediatric exclusivity and the purpose of the other list will be for the pediatric rule.

DR. CHESNEY: Thank you, again. That was very, very clear. Our next speaker is Dr. Rosemary Roberts, who is going to talk to us about waivers.

AGENDA ITEM: Waivers.

DR. ROBERTS: Well, I must say that I hadn't anticipated having such a presentation by a lawyer ahead of me that would be as good as Leanne. I have to compliment her heavily. Then she tried to steal my thunder by talking about the other list here. Okay, let's move forward.

I am going to speak to you today about the waivers under the final rule. I put this up here to remind you all that, not only are studies going to be required for drugs, but also for the biologic products, being very different than the modernization act, since most of those don't have any exclusivity.

I am going to make comments on full and partial waivers, the criteria for waivers, what we are calling the

preamble list, the process for waivers, the external review, and then items for discussion.

Now, a full waiver would mean that the sponsor was exempt from doing the required pediatric studies. Now, remember, we are talking about the final rule.

The only thing that we are looking at is the application in front of us. So, it is the drug product for an indication that is in front of us.

If a full waiver was granted for that application, it would be for that drug product for that indication. It wouldn't be for the entire active moiety, as was just discussed by Leanne.

A partial waiver would mean that they would be exempt from doing the required studies, in a specified pediatric age group.

If the condition didn't exist in part of the pediatric age group, you could be waived from doing studies in that particular part of the pediatric age group.

Now, what are the criteria for a full waiver? First of all, there would be no meaningful therapeutic benefit over existing treatment and it is not likely to be used in a substantial number of pediatric patients. Both of these would have to be fulfilled in order to get a waiver granted on this basis.

If the sponsor could show that they were unable,

or it was impossible or highly impractical to conduct the studies, that would be a basis for a waiver.

We have already heard a plea this morning from Mr. Westmoreland that we use this very, very sparingly, and that all attempts to recruit, if we need the information for this particular disease entity in the pediatric population, that all attempts to recruit patients have failed.

Lastly, if there is evidence that the product would be unsafe or ineffective in the pediatric population, we are not going to require studies in the pediatric population.

Now, partial waivers, what you are going to see is that these are very similar to the previous slide with some additional criteria.

Basically, it is no meaningful therapeutic benefit over existing treatment and not likely to be used in a substantial number of patients in a specified age group. So, you would be waived for a specified age group where there was no meaningful therapeutic benefit and no substantial use.

The studies are impossible or highly impractical to carry out in a specified age group, evidence that the product would be unsafe or ineffective in a specified age group.

Last, if, in order to study, say, an infant or

toddler, a special formulation was required, if industry had made reasonable attempts at trying to produce that formulation and failed, then they could be granted a waiver just for those age groups that needed that formulation.

Now, I have talked about meaningful therapeutic benefit. The regulation clearly defines what meaningful therapeutic benefit is.

It is defined as a significant improvement in treatment, diagnosis or prevention of a disease compared to marketed products adequately labeled for use in the relevant pediatric population.

We have already heard this morning that most products are not adequately labeled. A lot of products right now, since we don't have adequate labeling, may fit this definition.

Hopefully, several years down the line -- not too many -- we will be able to say, they don't fit it because we already have products adequately labeled.

I want to call your attention to significant improvement in not only the treatment of a disease, but in the diagnosis or prevention of a disease.

This is the preamble list. It is basically diseases for which there is limited applicability to the pediatric populations. It is not really drug classes.

It was published in the Federal Register as part

of the preamble to the final rule. It includes 20 diseases.

This was actually put in in a response to public comment on the proposed regulation. Now, this is the preamble list and these are the 20 diseases that are listed.

If you look here, you can see that these are diseases where the signs and symptoms of the condition occur in the adult population.

A product that is developed to treat prostate cancer is not really useful in the pediatric population, because, fortunately, we don't see prostate cancer in the pediatric population.

There are several cancers that manifest themselves in the adult population, there is Alzheimer's disease, some infertility issues and some other neurologic diseases that, fortunately, do not occur in the pediatric population, so they don't require treatment.

These are conditions that, if you have a drug for one of these conditions, we are likely to waive the requirement for studies.

That is what the preamble says. It says if you have a drug that is being developed right now and is in the agency for amyotrophic lateral sclerosis, then you could actually refer to the preamble, that this is one of the conditions that is outlined in your further treatment.

Now, we put this up here, and again, it goes back

to the fact of a significant improvement in not only treatment, but in prevention and diagnosis.

The list that is out there is directed toward treatment of conditions where the manifestations present in adults.

One can foresee, as technology develops, that in some of those conditions listed, we might be able to diagnose that a patient is likely to have those manifestations as an adult and maybe be able to prevent that condition by treating the pediatric population.

Some of those conditions that are listed for treatment, if you had either an agent that was for diagnosis of that, or prevention of it, then you might be required to do studies under the regulation for those conditions.

Now, what is the process for getting a waiver. First of all, FDA can issue the waiver on their own initiative. That would be very simple. We would just tell you a waiver is granted, and if it covers the entire pediatric population or partial.

Remember, it would only be for the drug product that is under review.

The sponsor may request a waiver, and if the sponsor requests a waiver, they must provide adequate justification that the waiver criteria that were previously outlined have been met. That needs to be brought in with

the request for the waiver.

Once that has been received, if the sponsor requests it, then the FDA looks at the information and either grants or does not grant a waiver.

This is outlined in the regulation, if the basis for the waiver being granted is because the product is either ineffective or unsafe for the pediatric population, that is useful information and it will go into the label.

Now, this is where the subcommittee becomes involved, because the regulation says that there is supposed to be annual oversight of the waiver process. Were the criteria appropriate for the waivers that were granted.

So, annually, we will be bringing this back to the subcommittee and we will seek advice and comment on the criteria used for the granting of the waivers.

These are just some things, if you have any comments on the preamble list that we just discussed, any general comments on the waivers, we would appreciate hearing those.

You can either give them today, or you have all seen the web site several times now, you can either call in questions to us at that 4-PEDS number. Any comments?

DR. FINK: On the preamble list, in general I would be in agreement with it. The only one I might question is arterial sclerosis, because I think there is

more and more data accumulating that that starts as an adolescent disorder, particularly in terms of prevention or early treatment. I wouldn't want to discourage studies in that area.

DR. ROBERTS: Clearly, if a sponsor had a product and they came in and wanted to study it -- and I think your example is good -- we would certainly encourage that.

It is just those kinds of comments we would like to have from people, if there are conditions up there that clearly either the entire pediatric population or a segment could benefit from studies.

DR. GORMAN: If a waiver is granted and then later, either off-label use or a new indication for the drug comes out, will it be possible to rescind the waiver?

I think of monoxidil, which came out of an antihypertensive but was shown to grow hair in a subsegment, which was certainly not in its initial labeling or marketing.

If something similar to that happens with pediatric patients having a potential positive outcome, is there a process envisioned, at least, in terms of rescinding the waiver.

DR. ROBERTS: So, in your example, if monoxidil had come in and gotten the hypertensive claim and we had granted a waiver there and then it came back with the hair?

DR. GORMAN: No, you said as an example something that had a completely off the wall, from my perspective, indication.

Perhaps a drug for Alzheimer's shows to have some ability to increase the cognitive function in children's with Down's Syndrome, to give a possible connection.

How would you go about rescinding the waiver to have the studies performed in children?

DR. ROBERTS: Under the regulation, it is an application that we have in house we can require studies on, for the indication that is in house and the drug product that is in house.

When it came in as the Alzheimer's drug, we would have given it a waiver for Alzheimer's. Now, if they come back in for cognitive function, they would be required to do studies for that indication.

The other thing this regulation is to do is to make thinking about pediatrics and pediatric drug development a part of the development of the drug.

This product would be being developed and, if that kind of information was there, then certainly the divisions would start talking to the sponsor about doing pediatric studies on cognitive function in children.

The only way we can require the studies under the application is on the application that is under review for

that application.

DR. MURPHY: I think, Rosemary -- let me see if I have got the question. They came in for an indication that had nothing to do with kids, they got approval. Now we have got a new indication.

I think what Rosemary is saying that if they came in with the same chemical, if you will, but they came in for a new indication, then they would come under the rule for that indication.

DR. GORMAN: I am not making myself clear because of the word indication. I am talking about off-label use, which occasionally drugs get used for and occasionally in adult medicine, I understand, as well.

If there is an off-label use in pediatrics, is there a way for this advisory committee or the FDA to rescind the waiver.

Much like in the orphan drugs products, there were off-product uses that rapidly increased the population to above the number of 200,000.

I don't think there is a mechanism in place to rescind the orphan status. Is there a potential mechanism if that situation arises.

DR. MURPHY: Again, our harping on the has to be in house is I think what you are trying to get at. If it is not in-house, and yet we know that it is occurring, could we

go out -- what it comes down to is, would we arrive at the conclusion that this marketed drug is now being used, and there is a meaningful therapeutic benefit to be gained that, if we don't label it, will pose a risk -- remember that criteria -- and there is a substantial use.

In that set of circumstances -- am I correct, Leanne, have I got this straight or not? Go ahead, say it aloud. We will work together here.

MS. CUSUMANO: Unfortunately, there is no way to get at off-label uses under the rule.

DR. MURPHY: That is right, it is exclusivity.

MS. CUSUMANO: The way to get at it is to try to get them to want the pediatric exclusivity. Under pediatric exclusivity you can request off-label indications. Under the rule, there is not, I mean, if a manufacturer decides that they don't want to market a product for a particular indication.

DR. MURPHY: So, the bottom line is, we would have to go out and ask for it under exclusivity.

DR. ROBERTS: One clarification, though, we wouldn't have to rescind the waiver, because the waiver would have been for a particular indication. It wouldn't have been for the entire drug.

MR. WESTMORELAND: If I may -- and I don't know my true status at this table at this point -- in the comment

period on the rules, some organizations suggested -- let me back up.

The FDAMA legislation included the provision that allowed companies to promote or disseminate information on off-label uses for drugs.

To do so, the companies have to file with the FDA a promise that they will, within three years, file a supplemental indication for the off-label use.

Some of the people commenting on the regulations, some of the children's advocates, suggested that any drug that was approved for the promotion of off-label use, or dissemination of information on off-label use be required also to develop the pediatric indication for the off-label use, if it seemed appropriate.

That part, I think Leanne is correct. That part was not included in the final rule, and I think that the agency decided to look only at primary indications and not at off-label indications, even though I think there is that window of opportunity when a company applies for permission to disseminate off label. The agency chose not to adopt that as part of the final rule.

DR. ROBERTS: Any other comments? Thank you.

DR. CHESNEY: Thank you very much. That was also extremely clear, Dr. Roberts. Our last speaker is Dr. Monica Roberts, who is a medical officer with the

division of anesthetic, critical care and addiction drug products, also in the Center for Drug Evaluation and Research. She is going to speak on the timing of initiation of pediatric studies.

AGENDA ITEM: Timing of Initiation of Pediatric Studies.

DR. MONICA ROBERTS: Good afternoon. I am formally trained as a pediatric anesthesiologist. I am not a pediatrician, as most of you are here today.

However, the issue of pediatric public health is something that is very near and dear to my heart. I can say with all sincerity that it is a privilege to be part of this learning process with you today.

I will be discussing with you the issue of timing of pediatric studies in relation to adult studies. My discussion will be centered around several guidance documents that have been drafted by our colleagues in the pediatric drug development arena around this subject.

When I was deciding on the best approach for presenting this topic to you, and remembering that I was scheduled for the second half of the second day of a series of a series of lectures, I thought you would enjoy images more so than text.

I searched the web for images that I thought spoke a thousand words.

When one asks the question, why invest the time and expense in doing clinical trials in pediatric populations, this image of an immature infant answers resoundingly that there are definite differences between children and adults, in the area of pharmacokinetics, the area of pharmacodynamics, the specific pathology of children and, obviously, in growth and development.

As we can see here, there is a wide range of patients that make up our pediatric population, each with its own special needs and medical concerns.

Finally, I think the National Cancer Institute, which coordinates the government's cancer research program, does the best job of answering the question, because lives depend on it.

I could go on and on about the importance of pediatric clinical trials, but I think we all wouldn't be here today if we didn't share my point of view on the subject.

Moving on to a discussion of the timing of clinical trials, as you recall, the 1994 rule allowed sponsors to simply gather adequate data on safety and efficacy of their product in pediatric populations, without the requirement for controlled clinical trials.

However, the 1998 rule mandated that studies be conducted for the indication in the product under review.

Furthermore, it recommended that a discussion with the FDA be conducted, and the initiation of pediatric studies occur at certain key phases of drug development, at the end of phase I, for most indications, and even earlier for life-threatening disease.

As a reminder, I have included a table of different phases of drug development and their purposes. Please keep in mind that there are variances on this general theme.

As you can well imagine, there have been many interested parties who have tirelessly devoted their time and resources to this initiative, one of which is the American Academy of Pediatrics.

I have highlighted for you -- I emphasize the word, highlighted. There is a wealth of information in this document I have not included in my discussion of it.

However, with respect to the issue of timing, the academy holds that the key elements to consider when initiating pediatric studies is, one, is there a therapeutic need for the product and, two, are there suitable formulations available.

There has also been international attention paid to this subject. The international conference on harmonization has been ongoing since the early 1990s.

The primary participants are the United States,

Japan and the European Union. Other countries, such as Canada and Australia, come as guests and as special participants.

They try to create harmonization on issues of drug development, including such issues as chemistry, manufacturing, preclinical and clinical trial design.

In September of 1998, the pediatric steering committee agreed to harmonize, which means that the participants agreed to draft, sign and act upon a pediatric document.

This group of experts from around the world emphasized flexibility when timing clinical trials. In cases where the medicinal product is intended to treat a disease which affects children exclusively -- for example, surfactant for respiratory distress syndrome in premature infants, or products targeted for genetic or metabolic diseases unique to children -- studies may be initiated with little or, in some cases, no prior adult exposure.

However, in those products intended to treat disease which mainly affects children, or has particular gravity in children, or have a different national history in children, the ICH participants agree the studies may begin following initial safety and reasonable evidence of efficacy.

In the case of life-threatening disease, where

there may few or no therapeutic options, they agreed to begin early in drug development, usually as soon as there is reasonable evidence of efficacy in adults.

However, one must consider the caveat in this. The majority of drugs in development never make it to the point of approval for human use.

So, in the case of a drug product that proves to be ineffective, too early initiation of testing in children may not prove to be wise either.

The ICH document stressed six factors to consider when timing pediatric clinical trials: the potential need for the pediatric formulation; the severity of the condition; the availability of alternative therapies; prevalence of the condition; knowledge of the safety profile of the drug or the lack thereof; the age range of the children to be treated.

Moving on now to a discussion of each of these factors, the first is the potential need for a pediatric formulation.

The need for suitable formulations is represented by this picture, of this sweet, little baby girl who will likely recreate the scenario of Dr. Jekyll and Mr. Hyde if forced to swallow a bitter, alcohol-based syrup, or even the contents of a capsule so carefully hidden in applesauce by her loving mommy.

The ICH group recognized the difficulty and extended length of time associated with the development of pediatric formulations.

Therefore, they recommended thinking about this early in the drug development process.

They concluded that the process of international harmonization on the acceptability of formulation excipience and validation procedures will help to assure worldwide availability of appropriate formulations.

Severity of the condition. Unfortunately, some children are born with life-threatening diseases, which require us to respond emergently, both in the area of medical care and drug development.

In this case, the committee agreed that studies may proceed following simply efficacy evidence in adults.

Availability of alternative therapies. The world of molecular genetics has exploded in terms of its ability to facilitate the diagnosis and treatment of disease.

New technologies in cytogenetics -- for example, fluorescent in situ hybridization to detect chromosomal microdeletions -- has led to improved diagnosis and treatment of certain causes of disability in children.

The ICH participants stressed the importance of keeping the efficacy, adverse event profile, and suitability of formulations of these and other alternative therapies in

mind, when designing drug development strategies.

Prevalence of the condition. The pediatric market for many drug products is small, which in many cases has hampered progress in the development of medicinal products for orphan pediatric patients, for example.

The ICH participants agreed that several approaches need to be explored to encourage development of products for certain select pediatric populations.

New molecular entity versus marketed therapy. There may be unique developmental safety concerns about a product, including non-clinical safety concerns which, in the case of a new molecular entity, may be unknown.

However, for an established therapy, the ICH participants agreed that these and all other safety data should be available and included in deliberations on the timing of clinical trials.

Age range of the children to be treated. Here, again, they stress the importance of flexibility when considering the age range and developmental stage of the patients being treated.

More emphasis should be placed on scientifically-driven study designs, even if they alter existing age categories. I think we were addressing this issue just previously.

The basic ethical principle of achieving the

desired data with the minimum number of patients should override any decisions to break the pediatric populations into too small, arbitrary age groups.

Finally, the ICH draft document stated that, throughout this drug development process, justification for the timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities.

The document concurred with the final rule, in concluding that it may be helpful to discuss pediatric clinical programs with regulatory authorities at an early stage of drug development, rather than later.

Also in agreement with the rule is a statement from the ICH document, that the product labeling should be clear and reflect available data.

Other significant guidance documents from our colleagues in this initiative are the draft document of the AAP, previously discussed, the Australian, the Canadian and the European documents, which are all consistent with the ICH recommendations.

- The following two points summarize the main points of these documents. One, early discussion with regulatory authorities, and early attention to formulation development.

In conclusion, the operative principles from all the documents I presented to you today, and those to consider when timing clinical trials in pediatrics are, one,

if the indication is similar in adults and children, initiation of pediatric studies may proceed following the end of phase II in adults, in the case of non-life-threatening indications, or following the end of phase one for life threatening indications.

Secondly, if the indication is unique to children, it is acceptable to initiate studies with little or no adult exposure.

As points of discussion for today or later, are the following two questions.

What, if any, are the circumstances where the initiation of pediatric studies should be delayed.

Secondly, what, if any, are the circumstances where drug exposure should begin in older children and then proceed in a descending chronological order, and not on the basis of projected need in any one particular age category. Thank you very much. Any questions?

DR. CHESNEY: Does the committee have any comments in response to Dr. Roberts' questions?

DR. MURPHY: Joan, you know, after the committee responds to these questions, we do have some time and we said, if we did, we might want to open it up to the audience in general, just for comments also. So, after the committee has its opportunity.

DR. CHESNEY: Okay, thank you.

DR. MURPHY: So, we take it that, off the top of our head -- and we don't expect final answers, again, as was explained. We will be bringing these topics to you, but are there any circumstances where the initiation of pediatric studies should be delayed, unless in the last 30 seconds nobody can think of one?

DR. O'FALLON: I have been impressed by the thoroughness with which the FDA has been considering this issue.

You have given us, over the course of the two days, a wealth of information. So, it is almost if we saw something, we can almost not believe that you haven't thought of it first.

In response to Dr. Roberts' last comment, I did have an immediate reaction, which let me throw out on the table and maybe get some discussion going.

It seems to me that there are some indications -- I mean, there are some diseases that tend to develop later in childhood. You just don't see it in the really little kids, but they tend to develop later.

It certainly would seem like that would be the kind of disease, or a treatment for that, would be the one in which you would think in terms of maybe taking the older level and not worrying about the younger ones.

In other words, you would want to split the

pediatrics into meaningful groups, depending upon the conditions. Does that seem reasonable to the physicians?

DR. FINK: It seems reasonable to me. I think there also would be circumstances where, looking at the disease entity, you might want to actually do the opposite.

If you look at treatment of a disease like asthma, our biggest need is actually to develop drugs that could be administered orally to children who are too young to use inhaled devices.

Oral alternatives to inhalers, potentially, you could make the argument, should be studied at the younger child and then later in the older child where there are more therapeutic options.

So, it may actually be disease and entity specific in both directions.

DR. LUBAN: I would support that. I can easily see, for example, in diagnosing and treating genetic disorders, you would clearly want to start early, not later. You would want it absolutely reversed.

DR. HUDAK: I guess in answer to Dr. Roberts' question about, can we conceive of any circumstances in which pediatric studies should be delayed, I guess I would just comment that to the extent that drug will be used -- and that is known ahead of time -- in a pediatric population, once the drug is released, I think the pediatric

drug studies should be done.

Otherwise, I think we are back in the situation where we are essentially doing an uncontrolled experiment in the pediatric population and sort of flying by the seat of our pants. I can't anticipate delaying studies in that situation.

DR. DANFORD: In addressing the second of the discussion points, are there circumstances where we should test the drugs in older children before younger children, perhaps there are, if there are chemical similarities of the drug in question with drugs known to have impact on developmental issues, specific to younger children.

Myelinization, you might want to test that in somebody who is not actively myelinating their nerves first, before tackling the riskier issues. There are also issues of bone development that are impacted by some drugs.

If you had some scientific reason to suspect that the risks were higher in young children, you might wish to defer that.

DR. FINK: One can also make, though, the exact opposite argument. If there is a significant toxicity and the drug may be used in that age group off label, it becomes more important to actually identify potential toxicities in age groups in which a drug is inappropriate, rather than to identify the age group in which the drug is safe and

effective.

DR. DANFORD: Well taken.

DR. HUDAK: I think I would like to follow up on Dr. Gorman's point about the expanding use of drugs and understand the sort of limitations of the legislation now.

I think what Dr. Gorman was trying to articulate is, if a drug was going through the NDA process and had basically been granted waiver status because there was no anticipation that the approved indication would be useful in children and then, after the drug is released, some other use is found for the drug in children.

This happens quite frequently in my area in the intensive care nursery, where drugs that were released with anticipation that it would be an adult drug suddenly find all sorts of uses in the neonatal population.

Once the cat is out of the bag, it is impossible, I guess under the current legislation and rules, to sort of ask for more information on the population in which the drug would be used.

I think that would be something that, in terms of your tracking in the future, you might want to see how often that occurs.

Resources like the pharmacy data bases sort of tell you how often these drugs might be used in pediatric populations, and I think it would be useful.

The second comment I have, I guess, is one that refers to, or would talk about the type of studies that are done.

I think developing studies in all pediatric age ranges presents some unique problems, in particular, with regard to safety issues.

We worry all the time in the nursery about, when we use a drug, and we are using this drug in children who are as young as 24 weeks gestation, where there is a lot of activity going on in developing and maturing different organ systems, whether or not that drug might have some impact, long term, particularly on the neurodevelopmental outcome of that child.

At least in terms of our profession, there is quite a bit of activity among neonatology in terms of looking at the long-term side effects, which can go out to even school-aged times.

Requiring pediatric information in that age range, I think, requires maybe some special phase IV type commitments to looking at that safety information, which I think needs to be understood and addressed.

DR. GORMAN: In terms of answering discussion point number two, an area where leapfrogging of chronological age groups may be important is where the therapeutic options are all bad that are presently used off

label.

Thinking of seizures in children between the neonatal age range and age six, we have one we use which makes them dumb, one that we use that makes them ugly and another one we use that gives them liver failure.

The concept of having both safety and efficacy data on some of the newer anti-epileptic agents might be real important for people who care for those people, and not in a lock step order going from adults to neonates, but starting at the neonates and the young children and working back up.

DR. MURPHY: I think that is one of the important things. Again, it comes back to, not only are there questions about the physiological and developmental changes, but where is the need also. It may not be where we sometimes think it is.

DR. EDWARDS: In terms of answering that first question, I think it will be an interesting and challenging time to make certain that the preclinical studies are very relevant to make certain that the drugs are safe.

Also, with the advent of elucidation of much of the molecular genetic code of humans, it may also be very important to look at issues of molecular mimicry that pharmaceuticals may have with genetic substances of the host.

I think that maybe there needs to be some innovative thinking about preclinical trials and thinking a little bit out of the box of what they have been doing prior to this time.

DR. CHESNEY: I think you make an excellent point. I know one of the issues that one of our faculty has been working on for a long time is a streptococcal vaccine.

Obviously, there are many issues involved in testing that in any age group. I think the issue of molecular mimicry comes into play here.

I am trying to find -- and I can't here -- one of the speakers talked about some of these issues with respect to diagnosis.

I hope this isn't too far off what we are talking about, but in terms of looking, for example, at tests that would screen children for the potential of developing breast cancer, I think there are many, many ethical and other issues there that might postpone such tests for children.

DR. MURPHY: Actually, that is one of the reasons we made such a point of this, is that, one, we want to make clear that it wasn't just for therapy, that we have to look at all three of these categories.

When you get into some of these other categories, you get into another additional set of concerns and questions that are different than just for the treatment.

I think that long-term follow up comes in various forms. It is one of the things that we are trying to deal with, particularly as we deal with asking for, in the written request, what it is that we want to know.

It is unreasonable to say we want to issue a written request where we want to know the answers 10 years from now. That would delay the whole developmental process.

Somehow, we are working with the sponsors, and how can we set this up so that we all know what happens 10 years from now, and looking at some of these ways of making phase IV more effective for everybody.

DR. EDWARDS: I think one other issue about the phase IV is that there is a lot of funding -- not enough, but there is some funding -- to look at phase IV adverse reactions to vaccines.

It might be possible that you could couple investigations looking at pharmaceuticals in addition to biologics in the same phase IV population.

DR. FINK: I think we bear the danger of becoming a little too paternalistic if we start saying we want to withhold diagnostic information.

Number one, the studies have shown that, once the tests become available, they tend to be utilized, whether they are approved in an age group or not.

Second, I think the range and the uses of

diagnostic testing are often hard to fine. If you take the example of the BRAC genes for breast cancer, you might have a mother who would argue that that would affect her decision of how many children she might have, if she knew that it was carried in a child.

For a young teenager, it might alter their reproductive decisions in terms of, at what age do they choose to bear children, before they get into a time of risk.

Dealing with cystic fibrosis, I have seen parents who wanted prenatal diagnosis, even though they would not consider intervention. They just want to know and be at peace with the decision.

I think we have to be careful and not be overly-paternalistic there and denying people access to diagnostic studies.

I think the reality of it is, we can't deny it anyway. Once they are available, we see the prenatal geneticists using everything that is available, no matter whether it is authorized or not.

DR. CHESNEY: I agree, but maybe there could be stipulations made that counseling has to be available or -- it is a very complex issue.

Are there any comments from the audience? Questions?

DR. GRINDER: Early in Dr. Roberts' presentation, she emphasized the value of pediatric formulations, especially in doing pediatric studies.

I hope that earlier I emphasized the importance of pediatric formulations, period.

The way the pediatric rule is written or the way the FDA has established the rule is, if there is an anticipated use less than 50,000 patients per year, a waiver will probably be granted.

For new chemical entities, that means there probably won't be a pediatric formulation coming to market for the thousands of children that don't total 50,000.

Certainly, for those products that are on the market that are generically available, there is no hope of ever having a commercially viable pediatric formulation available to the medical world.

There are other options that I wish the FDA would consider, and maybe some interpretation or reaction to this option is requested.

If there is not significant use, but clearly there is use, can the FDA require the manufacturer to provide information in the labeling regarding formulations, extemporaneous formulations for those products, so there is consistency throughout the pharmacy community for preparing such products?

MS. CUSUMANO: Pharmacy compounding is one of those things that FDA finds a difficult issue. I am not involved in the pharmacy compounding initiatives in our agency, so I don't know very much about it.

I know that there were some new provisions in the modernization act that talk about pharmacy compounding.

Obviously, the preference would be to have a stable, marketed formulation in the pediatric population. Sometimes there is no enough financial incentive for that.

Is it better to know, you know, how to compound it versus not to know anything at all? Probably, but it is something that we talk about internally, and I don't know that we are at a point where we have an answer.

DR. MURPHY: If we think a formulation is needed, certainly -- I am talking about under exclusivity now -- we are going to ask for it.

We have asked for it and companies come back in and say, now, here is what the problem is. We have said that we would look at compounding, actually doing the study with some compounding.

Now, that situation arose after it was clear that there was a reason that they felt it could not ever be made into a marketable product.

I think that one of the things that we are also concerned about is creating a product that is used in

studies and then never is marketed.

There are a number of things that we are going to need to be looking at here. As you can tell, we don't have the answers, or we wouldn't need all of this help.

We want these issues -- they will be coming up for further discussions. There may be a product where we may have to say, that is the way we are going to do it and try to define it, because there is no other way to do it -- in other words, some form of compounding. We will request where we think a formulation is needed.

DR. ROBERTS: I just wanted to comment on Mr. Grinder's comment. He said for many conditions there may not be 50,000 patients, so there wouldn't be substantial use, so a waiver would be granted.

Remember, to grant a waiver, there has to be no meaningful therapeutic benefit for the product and no substantial use.

So, if the condition was in less than 50,000 patients but there was a meaningful therapeutic benefit, as defined previously for the product, then we would not grant a waiver under that criteria.

DR. FINK: This is probably far too simplistic to ever be practical, but it would seem like it would make some sense to require that all marketed drugs have a liquid formulation available.

It is not just the pediatric indication. There is also widespread geriatric usage, there are gastrostomy tube feedings.

One could even go so far to say that it wouldn't be too far outside the realm of possibilities to bring an ABA action against a pharmaceutical manufacturer who didn't make a liquid preparation available.

We kept seeing other disabilities, like inability to swallow pills, be upheld by the courts. I think the liquid preparation really is a substantive issue, for convenience, for safety in particular, and really not uniquely pediatric. The geriatric age group is also a very large population that is underserved.

MR. WESTMORELAND: If I may, first in responding as you also did, I would also say that it would be unusual for a waiver to be granted in the situation in which there was any therapeutic value whatsoever to the new drug.

Second, in this area, even if a waiver is granted, that only means that it is not subject to the rule. It does not mean that it is not eligible for exclusivity.

If the company found it to be profitable in any fashion to get six months of exclusivity for this drug for adults -- remember, it is not just exclusivity for the pediatric use; it is exclusivity for the entire range of sales of the drug.

If the company were to find that they would like to enjoy the six months of exclusivity of monopoly profit during that time period for their adult sales, they may very well come in and ask for exclusivity on the basis of developing a pediatric formulation.

Secondly, I didn't want to be confused earlier, that the drug is not covered by the rule because it is an off label use of the drug and the FDA has not granted itself the authority to require the drug to be studied, it is still eligible for coverage in exclusivity.

Again, if it is an off label use for a drug that has been approved for another purpose, it is still eligible for exclusivity, and the company may choose to follow the incentives to come in for exclusivity as well.

Finally, in response to that last question, I don't think an ADA action will lie against a drug company. They are not performing any public service in this instance. It is not employment, it is not state action.

So, while I agree with the sentiment that it should be available to people with disabilities, I don't think an ADA action will fly

MS. NATASHA LESKOUSEK: I am wondering if the committee would comment on the risk of initiating pediatric studies prior to post-marketing use of a drug in a wider population.

Just recently, the endocrine and metabolic drugs advisory committee held a safety hearing on post-approval safety data for rejelin(?), an antidiabetic drug.

It showed a serious adverse event that was rare but, in the clinical trial population, hadn't occurred, but in post-approval data, did occur.

DR. MURPHY: I think that we are here today because one of the previously proposed -- I am not saying you are saying this -- but approaches was to use adults as a safety screen for products for children.

After you have seen enough adults and no one has dropped over dead, then it is okay to go into children.

I think the issue here is that we are taking a higher risk by not going through that process, if one believes that there are risks in continuing to treat children without information, if there has been off label use, and that has been the experience.

The experience is that children will end up getting that product along with the adults and we need to -- if we think there is potential use in children, we need to be looking at it.

I think you bring up a very good point, though, and this is one that concerns all of us. As we go forward and more and more products are studied in children, it is almost statistically predictable that some drug that really

is -- you know, is going to have a terrible, but rare, adverse event and may have a child as the first person that manifests that first but terrible adverse event.

Then, how are we all going to deal with that. So, you are right, that is a risk, but it is weighing against more than 20 years exposure to therapies, and what we know will continue to be exposure to therapies without having any information on how to treat children.

MS. LESKOUSEK: I guess one of my questions, then, is whether, if there has been long-term off-label use of an approved drug in children now, whether a new molecular entity might perhaps pose more of a need for deferral or delay of studies, just to get some broader experience in adults.

DR. MONICA ROBERTS: If I can speak for the participants in the ICH document, I have to reiterate what Dr. Murphy said.

I think that the importance of clinical trial development in pediatric populations far outweighs any issues of safety that you may find post-marketing.

Those are if, in fact, the product is for non-life-threatening disease, if there are no other therapeutic options available or, in fact, if you have at least some safety and efficacy information available for those specific populations.

DR. MURPHY: I think also Monica had on a slide the fact that we will take into consideration -- and I think the sponsors in discussing with us -- a new novel product where it isn't a serious and life-threatening disease, and which we have very little information compared to another product.

Maybe it is a new NME, maybe as a class we have more information about it. All of that is going to be factoring into some of these decisions.

DR. MONICA ROBERTS: I think it is often the case that it is the phase IV phase of things, post-marketing that you actually find out that products have a problem, because they are exposed to wider ranges of patients.

I don't think that should freeze you when you get a new molecular entity, and waiving it until you get more data from other products, or similar products, because it is not really until you release that particular entity, or expose it to the children in the diseases that you are interested in, that you really begin to see what the product can and cannot do for your population.

DR. FINK: If we really believe children aren't small adults, though, we have to look at both sides of the coin.

I think, again, we are saying children are small adults, because we want adult safety data.

There are well-known drugs like ketamine, where its safety profile in children is very good, it is a useful anesthetic agent, but it is toxic in adults.

The amino glycosides are far less nephrotoxic in children than they are in adults. So, how many drugs do we deny children because we don't study them in the population where they may be useful.

Children are not little adults, and to say that safety in adults proves safety in children is really buying into that concept.

I think we have to throw that out and start afresh saying, there may be drugs that are more toxic or less toxic in a different population when studied. If there is a valid indication, then we should study them in those populations that would benefit.

DR. MURPHY: Excellent point.

DR. O'FALLON: I would like to get some more information, because I don't know. We have been hearing today that the physicians are treating the children pretty much off label, because most of them aren't approved.

In the phase IV studies, are the drug companies -- are the companies -- collecting adverse events in the pediatric populations if, indeed, the patients are being treated off label, of course?

Are they collecting that data or is that just

going out into the atmosphere where it is never being tabulated.

DR. CHESNEY: I would just make one comment about one specific drug. The quinolones, as everybody knows, are not approved in children under 18 years.

I was amazed to hear recently that 12,000 children under one year of age have received siprofloxacin, and we have no data.

We have no feedback other than if something very severe had happened and it had been reported voluntarily to the FDA. We otherwise have no data on the outcome of those 12,000 courses of therapy.

DR. GORMAN: I would like to follow up on Dr. Fink's statement that there are epidemics in children that will never be predicted by adult use, and chlorinphenocol is a recent example, and benzyl alcohol in neonatal formulations is another example.

It is not that it is an active drug, but it created a difficulty in children that would never have been predicted by phase IV post-marketing studies.

Under the principles of distributive justice, if we believe that children should benefit from drugs and therapeutic advances, there needs to be some acceptance that we are going to place some children at more risk doing these studies.

DR. CHESNEY: Thank you. I think Dianne made that point and that is not one that I had thought of earlier, but it is a very real fact.

DR. WEISS: I just want to follow up. In terms of reporting requirements for phase IV, and Dr. Edwards mentioned something about the vaccine adverse event reporting system, which is very good and very nice in place.

I don't think it is quite as good for all the other drugs and biologics that are not vaccine biologics.

There is a very active post-marketing reporting system, and the agency is actually in the process of clarifying and redefining some of the reporting requirements, to make them easier and more consistent with what needs to be reported premarketing.

It is confusing for a lot of us in the agency that don't deal that much with the post-marketing side of things.

There are specific requirements for anything that is a serious or life-threatening event, or resulting in death, or is an unlabeled event.

There is a requirement that those events have to be reported within 15 days of knowledge of the event to the agency.

Then there are also requirements for periodic safety updates. There are hefty requirements, more frequent reporting requirements in the first year or so after

something is approved than subsequently.

Those things come in, sometimes the data is not as complete as one would like, but they do try to capture information on concombinant medication, underlying diseases, age of the patients being treated.

So, you do see, even if the age is not an indicated age, you will get that information in your post-marketing reports.

DR. GRINDER: I would like to offer to the subcommittee another resource to use at some point in time, and that is the pediatric adverse drug reaction reporting program, which is coordinated by the Pediatric Pharmacy Advocacy Group.

The data that I have handy from that reporting program, found 712 adverse drug reactions reported in the first 10 months of 1997.

The participation in this data base continues to grow. It has identified significant trends in adverse drug reactions post-marketing that the Medwatch program wouldn't pick up.

I am sure that the data in that program would be readily available to this subcommittee.

DR. CHESNEY: Thank you for reminding us about that. I think, too, for many of us, and maybe I don't speak for anybody else but myself, when you have a complex patient

who is on a number of different drugs and you have an adverse event, it is very confusing as to whether that was related to a drug and, if so, which drug and/or was it part of the natural course of the disease.

I think there is often a reluctance to report, because it does mean filling out a lot of forms and the event may have nothing to do with a drug.

MR. WESTMORELAND: If I may continue on that point, there is an active debate in the legal literature about whether a passive reporting system, like that one just described, which I think is the best that the agency can do under the current circumstances -- and this is no criticism of the agency -- but whether a passive reporting system, for some of those very reasons that you describe, is good enough for detecting anything beyond phase IV for adverse events reporting.

I have seen also a very interesting study in the last couple of months about how physicians in managed care, despite the number of patients they may be seeing, report at two-thirds a lower rate than physicians who are in traditional fee-for-service medicine.

The thesis for the article is, indeed, that managed care physicians don't have time to figure our what the adverse event was, and what caused it and don't report it at the same rate.

I would suggest to this committee that is of particular concern, since a significantly disproportionate number of pregnant women and children in this country are on Medicaid and Medicaid has now, as of the balanced budget act of 1997 given all states permission to herd everybody except the special needs children into managed care participation, and questionable managed care participation in some states.

We may see less and less passive adverse event reporting, because more and more children are in Medicaid managed care organizations.

DR. CHESNEY: I think that is all extremely well taken. I think that is one reason that the pharmacy reporting system is so valuable.

I think most of us will call the pharmacist if we see -- I am talking about inpatient -- if we have an adverse event, could this possibly be, could you find something that I am not finding in the PDR.

I think that they are better about reporting those kinds of things than we are. So, again, I particularly thank-you for reminding us of that.

Well, if there are no other comments, Dr. Murphy, do you want to give us some final words of wisdom?

DR. MURPHY: Mostly, I wanted to thank the committee. I wanted to thank everybody who came here today to listen to this discussion, presentations, and to learn as

much as they could about the process of the implementation of both of the legislative and regulatory activities.

I want to tell you, the next time, the committee, we see you, we will have -- I am sure you will just have been able to have absorbed all of this completely, integrated and be able to respond with all these questions that we will try to scratch our heads over as to how we are going to answer them.

We will be bringing to you a more focused process, as far as it will be more narrow in some of the issues that we have before us.

We have tried to outline where we think some of those issues will be. We expect to see you again before next year.

We also wanted to remind everybody that the slides will be available from the talks on the web. I am told a week to two weeks, that they should be up there.

Again, thank everybody for being here today and participating in this activity.

DR. CHESNEY: On behalf of the subcommittee, I just wanted to thank all the speakers today. I think your talks were extremely lucid and we have all learned a great deal and we really appreciate all the preparation that you have put into today's event. Thank you.

[Applause.]

[Whereupon, at 3:15 p.m., the meeting was adjourned.]