FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEETING OF THE

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

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ALSO PRESENT:

THOMAS SCHAIBLE, PH.D.
Senior Director, Immunology Medical Affairs
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C O N T E N T S

P R O C E E D I N G S

(8:15 a.m.)

DR. SALOMON: Good morning, everybody. I'm going to open the meeting today. My name is Dan Salomon, and I'm a member of the Scripps Research Institute in La Jolla, California.

I'm going to act as the acting Chair today. It just seems a little strange to me -- I've already noted that -- with having Dr. Vose to my left who, ever since I've been on the committee, has been the Chairperson and basically been for me a role model for what a Chair should be of this kind of a committee. I can only be a facsimile of Dr. Vose. I've asked her to just sort of elbow me from time to time if I'm not doing it right. But anyway, I apologize. I really won't be able to do as good a job as she does.

The meeting today will start in a moment, but I thought what we ought to do, just to begin, is go around the table and introduce everyone and everyone just sort of briefly tell us what institution they are from and what their basic clinical or scientific interests are. If we can start on the left.

DR. O'FALLON: I'm Michael O'Fallon from the Mayo Clinic. My expertise is in biostatistics.

DR. CHAMPLIN: Richard Champlin from the M.D.

Anderson Cancer Center and the Chairman of the Blood and Marrow Transplant Department.

DR. SAUSVILLE: I'm Ed Sausville from the National Cancer Institute and the Developmental Therapeutics Program, and my interest is in the development of new drugs for the treatment of cancer.

DR. VOSE: Julie Vose from the University of Nebraska Medical Center, and my research interests are in lymphoma and hematologic malignancies, transplantation, and immunotherapy.

DR. SALOMON: Again, as I said, Dan Salomon, Scripps Research Institute. My interests are in transplantation, xenotransplantation, and gene therapy.

MS. DAPOLITO: Gail Dapolito, Executive Secretary for the committee.

I'd also like to announce that Dr. Richard Goldsby from Amherst College is participating on the speaker phone this morning.

I'd also like to take this opportunity to introduce Ms. Rosanna Harvey, the committee management specialist. As the committee knows, Rosanna was instrumental in the preparations for today's meetings, and as usual, she'll be around all day to help out with any questions.

Thank you.

DR. BROUDY: I'm Virginia Broudy from the University of Washington, and my interest is in hematopoietic growth factors.

MS. MEYERS: Abbey Meyers, President of the National Organization for Rare Disorders, which is NORD. I'm a former member of the committee I believe and a consultant today for consumers.

DR. MILLER: Carole Miller from Johns Hopkins. My interests are in hematologic malignancies and bone marrow transplant, clinical.

DR. STEIN: Kathryn Stein, Director of the Division of Monoclonal Antibodies, CBER.

DR. SCHWIETERMAN: Bill Schwieterman, Chief of the Immunology and Infectious Disease Branch, CBER.

DR. SIEGEL: Jay Siegel, Office of Therapeutics at CBER.

DR. SALOMON: Yes. I'd also like to add that Dr. Hugh Auchincloss from Harvard Medical School will be joining us in a few minutes.

Next Gail will read into the record the administrative remarks.

MS. DAPOLITO: This announcement is made part of the record at this meeting of the Biological Response Modifiers Advisory Committee on July 15.

Pursuant to the authority granted under the

committee charter, the Director of the FDA's Center for Biologics Evaluation and Research has appointed Dr. Virginia Broudy, Ms. Abbey Meyers, and Dr. Julie Vose as temporary voting members for the committee discussions.

Based on the agenda made available and on relevant data reported by participating members and consultants, it has been determined that all financial interests in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee's discussions have been considered. The following participants have been granted waivers, in accordance with 18 U.S.C. 208, which permits them to participate fully in the committee discussions: Drs. Hugh Auchincloss, Virginia Broudy, Richard Champlin, Carole Miller, and Julie Vose. Dr. Michael O'Fallon has requested to be recused from the discussion of the report of the Xenotransplantation Subcommittee.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in

today's committee discussions. Copies of the waivers addressed in this announcement are available by written request under the Freedom of Information Act.

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

DR. SALOMON: Thank you, Gail.

Are there any other comments from the FDA staff we need to deal with?

(No response.)

DR. SALOMON: I'm going to, as Chairman, try and stay on time but, in the same way, allow everybody to participate in the discussion as much as possible.

Obviously, for recording interests, it's going to be important for us, as usual, to make an effort to speak directly into the microphones. I apologize if we have to remind anybody of that. I usually forget myself.

Then I'd like to open up the public hearing. We have one scheduled speaker which is Dr. Thomas Schaible, Senior Director of Immunology and Medical Affairs for Centocor. Welcome, Dr. Schaible.

DR. SCHAIBLE: Thank you. Good morning. We appreciate the opportunity to share our experience at Centocor regarding immune responses to therapeutic

biologics.

This morning I'd like to touch upon a few of the key issues revolving around immune responses and, more specifically, share with you our experience with two of our products, Remicade and ReoPro, and then finish up my presentation with some conclusions based upon that experience.

Now, certainly one of the key issues with biologics is their potential antigenicity, and if antibodies develop against these agents, what is the clinical relevance both in terms of safety, whether there are potential allergic reactions or hypersensitivity that may result from these antibodies, but also in terms of efficacy, is there potential for blocking antibodies that may result in reductions in potency of these agents.

I think as a quick background, it's important to recognize that a number of biologic agents, both recombinant molecules, as well as monoclonal antibodies, do develop antibodies at varying incidences as well as magnitudes.

Now, in terms of our own experience, I'll focus on our two products: Remicade, which is infliximab, and ReoPro, which is abciximab. I think it's important to point out some important differences in these products both in terms of the molecules themselves, but also in terms of

the diseases in which these agents have been developed.

First of all, with Remicade, Remicade is a whole chimeric IgG. It has a long serum half-life of approximately 10 days. It has been developed primarily in the treatment of chronic inflammatory disorders. Therefore, multiple dose regimens have been a key part of that development, and it has been used both with and without concurrent immunosuppressive agents.

With regard to ReoPro, abciximab, it is a chimeric Fab fragment. It has a short free serum half-life, less than 10 minutes. In part, that's due to the fact that it immediately binds to platelets after it's administered intravenously. It has been developed for treatment of acute coronary syndromes, and as such, it has been given primarily as a single dose, but it's important to recognize that because of recurrence of these types of syndromes, there's clearly a potential for readministration of this agent.

In terms of the development of Remicade in chronic inflammatory diseases, we have extensive clinical trial experience now both in Crohn's disease, which is an inflammatory bowel disease, as well as rheumatoid arthritis, and this experience includes both experience with single-dose regimens, as well as longer-term repeated dosing regimens.

In terms of experience with single-dose regimens, in Crohn's disease, we have observed a 13 percent incidence of human anti-chimeric antibodies, or HACA. Generally these are of low titer, less than 1 to 80. The incidence is lower in patients who receive concurrent immunosuppressants such as Immuran, such as 6MP. This incidence is about two-fold lower in patients receiving concurrent immunosuppressants.

In addition, we have observed some delayed hypersensitivity events, but specifically this has occurred in patients who have had a long interval, that is, 2 to 4 years, between exposures to the agent.

Now, in rheumatoid arthritis, we have a more substantial experience with long-term repeated dose regimens. In these studies, doses were given at 0, 2, and 6 weeks, and then every 4 or 8 weeks thereafter. We have studied doses of 1, 3, or 10 milligrams per kilogram, and we have studied these doses both with and without current methotrexate treatment which is the immunomodulator that is currently one of the standards of treatment in RA.

Now, in our phase II experience, we observed that both dose and concurrent methotrexate treatment were important in the incidence of HACA development. First of all, what we observed was that lower doses of Remicade were associated with higher incidences of HACA. In addition, if

Remicade was given in combination with methotrexate, this also had the effect of reducing the incidence of HACA.

Now, in our phase III program, because of these findings, as well as a number of other reasons, we selected to study doses of 3 and 10 milligrams per kilogram given in combination with methotrexate.

One of the key issues here is to establish how well these agents are tolerated over time when they are given repeatedly. I think our experience in our phase III trial, which is called the ATTRACT trial, has been very helpful in getting a better understanding of this.

Here I'm showing data for infusion reactions. These are adverse events that have occurred either during the infusion or within 1 hour after the infusion. And here we show data for the incidence of infusion reactions when Remicade is given every 8 weeks or every 4 weeks. I think this data show that there is overall a low incidence of infusion reactions in patients over time, slightly above placebo rates, but only by a few percentage points. And more importantly, there's no trend over time for an increase in infusion reactions.

Now, what have we learned from this experience? First of all, antibodies do develop against Remicade. It appears it's in the 10 to 15 percent range. The incidence can be modified by several factors, including the dose, the

frequency of dosing, as well as whether the agent is given in combination with immunosuppressant therapies.

However, the clinical relevance of antibody development is still uncertain. HACA development is not predictive of subsequent hypersensitivity events, but more importantly, what we are observing is that long-term repeated treatment indicates that one can give these agents with sustained effectiveness, as well as the fact that these drugs are well tolerated given over the longer term.

Now let me focus in on the ReoPro experience. First of all, I think it's important to point out that the experience here is substantial, that we have done HACA measurements in over 6,000 patients in clinical trials, and this includes the EPIC trial, the CAPTURE trial, and the EPILOG trial, where with initial administration of ReoPro, we have observed an incidence of about 5 to 6 percent for HACA. Again, these are generally of low titer, less than 1 to 400, and there has been no increase in allergic reactions compared with placebo groups.

Now, in addition, we have undertaken a registry to collect data prospectively in patients who are readministered ReoPro commercially. This is a phase IV multicenter prospective registry which is being conducted in the U.S. It has now enrolled 791 patients, and in 579 of these patients, we now have data on HACA both pre and

post a readministration of ReoPro.

The objectives of this trial were, first, to determine the HACA incidence, its titer, and duration, as well as to evaluate safety and efficacy after readministration, and this would focus on adverse events, success of the angioplasty procedure, as well as in vitro assays of ReoPro potency.

Now, looking at the results for HACA incidence, following an initial administration of HACA in this registry, there was a 6.4 percent incidence of positive HACA. The median titer was 1 to 100. With readministration of HACA, there was an increase in the incidence of HACA, increasing to 27.1 percent with a modest increase in the median titer, going up to 1 to 400.

In terms of the durability of the HACA response -- that is, how long could it be measured in the serum -- it was generally 4 months or less.

In terms of major safety events in this readministration experience, there have been no deaths associated with adverse events, no allergic or hypersensitivity reactions, and no occurrences of intracranial hemorrhage or retroperitoneal bleeding.

Looking at the success of the angioplasty procedure, we can focus on the two yellow bars which show results for patients who were positive for HACA entering

the procedure and those who were negative for HACA entering the procedure. In both groups, there was a high success of the angioplasty procedure, and there was no difference as to whether a patient was positive or negative for HACA.

Then we have also looked in vitro at assays to measure the potency of ReoPro. Here we have taken normal donor platelets and added them to sera that is positive for HACA at varying titers. And if we look at the IC50 in these studies, there's really no apparent decrease in potency looking over a range of titers of HACA. So, it appears that ReoPro is still able to inhibit platelet aggregation in these assays.

So, what have we learned from the ReoPro experience? ReoPro is clinically effective when it's readministered. Readministration has not been associated with allergic or hypersensitivity reactions. And finally, a positive or a negative HACA titer is not predictive of clinical effectiveness or other clinical events.

Now, putting all of this experience together, these next two slides I think will summarize that experience. Development of immune responses to therapeutic biologics has raised the concern of increased allergic reactions and/or loss of potency. However, over the last 10 years, extensive time and effort have been given to developing and analyzing HACA responses and their effects.

We now, with over 8,000 patients in clinical trials and 5 years of post-marketing experience in over 500,000 patients, can conclude that, first of all, a large database of HACA measurements have been established and that antibodies can be detected in a relatively small proportion of patients receiving these agents.

However, the large clinical experience has also demonstrated that the immune response is modifiable by both dosing strategy, as well as concurrent medications. Readministration can be accomplished safely and without loss of efficacy. And in terms of the future, the focus should be on continuing pharmacovigilance of retreated patients rather than accumulating additional information on HACA titers.

Thank you for your attention.

DR. SALOMON: Thank you, Dr. Schaible.

I'd like to request any questions, comments, or discussion from the committee. Questions. Yes.

DR. SAUSVILLE: So, do you have any idea quantitatively, when you said there's a titer of X or Y or Z, what actual amount of antibody you're detecting in here? Is it micrograms or nanograms per ml? Has that been calibrated?

DR. SCHAIBLE: No, it has not been calibrated. We just haven't done those types of studies.

DR. SALOMON: Abbey.

MS. MEYERS: I'm trying to understand what you said in ordinary, plain English. These products seem to cause a reaction in a certain number of patients. Right?

DR. SCHAIBLE: That's correct.

MS. MEYERS: But you don't know whether that reaction is clinically relevant or not.

DR. SCHAIBLE: Right.

MS. MEYERS: For example, if they have antibodies, you don't know whether that means anything. Right?

DR. SCHAIBLE: That's correct. We have developed methods for determining the presence of antibodies, but the clinical relevance of those antibodies I think, based on our experience, is still uncertain, and it may represent the fact that there are a number of different types of antibodies that develop against these agents.

MS. MEYERS: But it doesn't mean anything if you rechallenge the patient later with the same agent. Right? I mean, they seem to respond just as well after they --

DR. SCHAIBLE: The majority of patients do. I wouldn't say that there are antibodies that are not clinically relevant. Certainly there are. We have seen

instances of patients who have been previously exposed to Remicade who then, on a subsequent exposure, very long after that initial exposure, have developed a delayed hypersensitivity event. So, we have seen instances of that. I wouldn't want to say that these are totally irrelevant.

MS. MEYERS: How serious has that been?

DR. SCHAIBLE: The events are manageable, clearly manageable. The events that we've experienced with Remicade have all been medically manageable and there have been no long-term sequelae of those events.

I think the issue here is whether these types of assays provide information that is predictive as to when these types of clinical events may occur, and I think our experience to date is that the predictive value of these assays is actually not very good either from a positive sense or a negative sense.

MS. MEYERS: So, you don't know which patients are going to have this reaction.

DR. SCHAIBLE: No. That's very difficult to determine.

MS. MEYERS: I see.

And the two products you're talking about, one is for Crohn's disease, the other one is for heart problems.

DR. SCHAIBLE: It's for coronary angioplasty.

MS. MEYERS: And yet, these reactions or these antibodies seem to appear the same amount in both products.

DR. SCHAIBLE: Yes. I think our experience overall is that they're in the 5 to 15 percent range.

MS. MEYERS: So, is this going to happen with most biological products?

DR. SCHAIBLE: I'd be interested to hear the committee's view on that one.

DR. SALOMON: Yes. I think, as usual, Abbey has done a great job of putting her finger on the key question.

(Laughter.)

DR. SALOMON: Jay?

DR. SIEGEL: Yes. I have a question.

You presented the data with in vitro testing I guess of IC50 in patients with high titer. One of the things that we see with some products -- and I don't know what the data are with your product. That's basically my question -- is that while there's not neutralizing or inhibitory activity of antibodies, that in patients with high titers of antibodies, the half-life changes considerably.

And so, the question is do you have pharmacokinetic data? And if there is a change in half-

life, does it correlate, as one might expect, with a change in the time until -- I guess in the case of ReoPro, there are sub-inhibitory levels of antibody on board.

DR. SCHAIBLE: Well, the experience with those assays so far is that we have experience only up to certain titers. So, you saw data up to 1 to 3200 titers. There is very limited experience beyond that because there are much fewer patients who have developed high titer responses. So, at least over that range of data, we have not seen any inhibition of potency. I really can't speak to whether, if you were to really boost the titer, that that might ultimately have an effect on potency.

DR. CHAMPLIN: My question was what fraction of these were neutralizing antibodies.

DR. SCHAIBLE: Neutralizing in terms of whether they bind to the portion of the drug that is involved in its effectiveness. Our experience is that most of the ones with Remicade are. However, with ReoPro, as I've shown you the data, it appears that they're not neutralizing in terms of the anti-aggregation effects in patients in terms of platelet function.

Yes?

DR. SAUSVILLE: I was simply going to enlarge on, I guess, the point that Jay was getting to. In other words, this issue is likely going to occur with,

quote/unquote, every biologic to one degree or another, but whether or not it's of clinical significance is a dose and nature of molecule type of thing. And I think it's going to be very difficult. I mean, it's very good that in your experience you appear to have efficacy and the events appear to be manageable. But to extrapolate from that experience to any other biologic, I think is going to be really difficult.

DR. SCHAIBLE: Right.

DR. SAUSVILLE: I think a key harbinger of potentially having an effect would be either, as you say, the neutralizing question or an obvious change in pharmacology. I think it's ultimately going to have to be assessed for each product.

DR. SCHAIBLE: Right. I would just add that our approach to this also is to gain as much prospective data post-marketing as we can, and that involves designing and implementing registries. You saw that with the ReoPro readministration registry. We're also just implementing now one in Crohn's disease because I think in the long term you want to know how these patients are responding clinically, both in terms of how effective the agents are and how well tolerated they are from the clinical perspective.

DR. SALOMON: Dr. Miller.

DR. MILLER: On the Remicade, what is your retreatment data? And the reason for that is with the data you showed here, you continue to have a response in decrease in swollen joints, and I think with many biologics that interfere early on in the blockade, you don't know how long the effector cells from the initial treatment are still affected. So, I don't think we really know how long you have to treat patients with some of these biologic modulators of the immune system.

So, my question is, since especially in the Remicade it appears to be neutralizing antibodies, number one, you don't know if those doses after the neutralizing antibodies are truly necessary for continued response. And so the only way you can get that is to get retreatment data on patients who actually had neutralizing antibodies.

DR. SCHAIBLE: Right.

DR. MILLER: Do you have that?

DR. SCHAIBLE: No. We have limited data on that.

One of the problems also is that with long-term repeated dosing, so long as the agent stays in the blood, it will interfere in the assay for antibodies. So, in fact, you have to wait a very long time until patients are essentially off the drug before you can get a valid measurement as to whether these antibodies are present or

not. And these trials are ongoing. So, that's the reason why we have limited data in terms of taking patients who have antibodies and then retreating them at that point.

DR. SALOMON: Do you have data on immune complex formation, and do you have data on complement activation in any of these patients after retreatment?

DR. SCHAIBLE: Very little, very little.

DR. SALOMON: Another issue that concerns me about biologics and repeated administration is going to be whether or not we generate neo-immune responses and generate auto-antibodies, for example, then which later can cause problems. I don't know that these antibodies are more likely than any other, but overall I think it's an issue with new therapeutics.

DR. SCHAIBLE: In terms of antinuclear antibodies or anti-double-stranded --

DR. SALOMON: Have you looked for, for example, anti-platelet antibodies after ReoPro administration? Let's say 6 months after these patients have been in the trial. Have any of them developed platelet auto-antibodies, and have you measured bleeding times a year, maybe, after repeated administration?

DR. SCHAIBLE: No. I know we definitely haven't measured bleeding times in that time frame. I don't know if we've look at any anti-platelet antibodies or

not. I'm not aware. If we have, I'm not aware of it. Sorry.

DR. SALOMON: I bring these up just because you were brave to get up.

(Laughter.)

DR. SALOMON: Clearly this isn't to discuss specifically your product, but I think the results you presented are very apropos obviously to the discussions that will happen this afternoon where we definitely want to grapple directly with what kind of assays should sponsors be developing. So, I hope you'll forgive --

DR. SCHAIBLE: It's quite all right. Thank you.

DR. SALOMON: Are there any other comments?

MS. MEYERS: There's some biotech products that have been on the market for a much longer time. Has anybody spoken to those companies and tried to get this data from them?

DR. SIEGEL: We'll be presenting some of those data in just a couple hours.

DR. SALOMON: Yes. There is an experience to draw from.

Dr. Goldsby, I don't want to exclude you.

DR. GOLDSBY: I have no questions.

DR. SALOMON: We're trying out this new

technology. I hope you'll forgive me if it seems a little awkward.

Are there any other comments?

(No response.)

DR. SALOMON: Well, then I want to thank very much Centocor and Dr. Schaible and his colleagues for this. I think it was an extremely informative presentation and will again, as I said, be very useful this afternoon. I hope you're staying around. You'll be here this afternoon. Excellent.

At this point, it's also appropriate to ask is there anyone else that would like to present anything to the committee before we close this portion of the committee, the open public portion.

(No response.)

DR. SALOMON: Then for the minutes, let me note that no one else wants to address the committee, and we are now therefore closing the open public hearing portion.

We would like to move on to topic I, the FDA Regulatory Policy Update, and for that I'd like to introduce our own Dr. Jay Siegel.

(Laughter.)

DR. SIEGEL: Thanks. I also would like express and add my appreciation to Dr. Schaible. I think, as you'll soon see, those data will be very useful and mesh

well with our presentation and planned discussions regarding immunogenicity and policy approaches.

What I'd like to do today and what actually Dr. Weiss and I will do in the next couple of presentations is update and inform the committee regarding some areas of active policy development. The last 2 to 4 years have been an extremely active period of time for the FDA vis-a-vis development of new policies and new guidances in many areas, in part spurred initially by the anticipation of Congress' development of the Food and Drug Administration Modernization Act of November 1997. After that act was passed, it mandated substantial additional policy and guidance development. It has been an active period, and it has impacted a number of areas that this committee and other committees and members of this committee as they sit often on other committees that we visit as well have frequently raised questions on and have shown a great deal of interest in.

So, we're going to pick out a few of those areas which particularly impact the deliberations of this committee vis-a-vis product approvals in terms of what is the standard for proving efficacy for biologics products, what is the nature and what's new regarding accelerated approval for products for serious and life-threatening diseases, and what are the recommendations and requirements

and guidelines regarding doing pediatric studies. Those of you who have been a member of this committee for a while know that those are issues that come up frequently, and there have been some significant changes for at least clarifications in all of those areas. I'm going to focus primarily on issues regarding the evidence of efficacy and then Dr. Weiss will be speaking specifically about pediatric indications.

Now, the 1962 drug amendments established a standard of effectiveness which has been applied, at least by the Center for Drugs and, to some extent, by the Center for Biologics over the period since that point in time. It says that effectiveness must be established by substantial evidence, and it defined substantial evidence to be "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and expertise" -- I omitted a few words there -- "on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effects it purports or is represented to have."

Although it may not show up, I bolded the letter "s" in "investigations." One of the most important phrases here is "adequate and well-controlled investigations," something that the Centers for Drugs and

Biologics look for carefully in studies. I bolded the letter "s." As a matter of policy, as well as court decisions, this was taken as a key indication that there needed to be more than one adequate and well-controlled investigation. There's now substantial legal and policy clarification on that issue which is one of the key issues that I'll be discussing over the next several minutes.

That was from the Food, Drug and Cosmetic Act. All biologics are, to my knowledge, either biological drugs or biological devices, but biologics are additionally covered by the Public Health Service Act which requires that they be safe, pure, and potent. There is substantial case record and legal support for the notion that potency means effectiveness, not simply biological activity.

But the linkage to the standard that I just read regarding drugs has, at least till recently, until FDAMA of 1997, been indirect. It's now more directly linked.

On the basis of these different legal approaches, there was, up until maybe five or six years ago, the widespread notion, with some basis in reality, that there was a requirement. It turned out that it wasn't an absolute requirement. But there was essentially a requirement for at least two adequate and well-controlled investigations for drugs and there was a perception, with

again some basis in truth, that biologics sometimes required only one efficacy trial. Indeed, the approach in Biologics was that the number of trials was just one of several indicators of quality and quantity of evidence, and it perhaps wasn't as carefully focused on as it was in the Center for Drugs, although certainly recognized to be important.

But there was concern both within the agency and outside, particularly as biologics began to be applied to and used for a broad variety of indications, many of which are competing against drugs in a similar indication, that there really ought to be some level of harmonization. Back about six years ago, Dr. Zoon and I and Bob Temple and Janet Woodcock and a few other people began talking and trying to come to a meeting of minds and discovered, in fact, that we had each evolved to a position that was not particularly dissimilar.

In 1996, the agency began an initiative to clarify, because there were a lot of misunderstandings, regarding what type of data are needed for a supplemental indication, for a new efficacy indication for an already approved drug. In doing that, we came to realize that that really needed to be broadened. There wasn't really a different standard, and many of the issues that applied to supplemental indications also applied to first indications.

This evolved into really work on an effectiveness guidance. It was published in draft in early 1997.

In late 1997, the Food and Drug Administration Modernization Act -- and I'll quote its passages -- essentially endorsed most of the concepts in that guidance. That was clearly the message from Congress as we met with Congress on these issues. The guidance was then, on the basis of public comment, finalized and formalized, and I'll be reviewing it shortly.

The Food and Drug Modernization Act has a section entitled Number of Required Clinical Investigations, and what it says is, specifically in clarifying the intents of the words "adequate and well-controlled investigations," "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence," substantial evidence being the legal standard. And the guidance document, again that I will summarize shortly, goes into significant detail to clarify what the agency considers to be appropriate confirmatory evidence in the context of this law. But it also addresses several other issues.

As I noted earlier, there are historically some

different approaches between drugs and biologics. The Food and Drug Modernization Act of 1997, a section entitled Modernization of Regulation included the following language. "The HHS Secretary shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the PHS Act," which is what we grant our biologics license applications, "and products required to have approved NDAs under section 505(b)(1) of the Federal FD&C Act."

A letter of congressional intent clarified the issue, as there was significant confusion, that this was not intended to change in particular different approaches to generics for drugs and for biologics, and it was also clear from discussion that different scientific issues raised by the different classes of products needed to be addressed.

But one of the issues that this was clearly intended to address is in fact the focus of my talk today, the efficacy standard, and lacking specific scientific reason for differences, clearly the message here is that such differences should be minimized or eliminated.

On the Biologics web site -- Gail, was the efficacy guidance document distributed to the committee?

MS. DAPOLITO: Yes.

DR. SIEGEL: It was, okay. So, the first document you have. There are a couple other documents I'll talk about which I didn't feel that you'd probably want to weigh down your briefcases with, but are readily available to you or anybody through the Internet. A whole slew of our guidance documents are at the site. The address is noted on this slide. The Center for Drugs has a site as well with extensive FDA guidance documents, some of which you might find interesting. These two documents are indeed on both sites as they and an increasing number of policy guidances apply equally to both centers.

The guidance that I'm going to focus most of this talk on, as I've said several times -- and I'll get to it soon -- is the guidance for industry on providing clinical evidence of efficacy for human drug and biological products.

I'll note here, although not specifically discuss, an additional guidance that we put out that really addresses how this general guidance applies specifically in the case of cancer treatment. It's entirely consistent, but it's a specific application in terms of more detail in the setting of oncology as to what the agency would and would not or might and might not consider adequate evidence of efficacy for cancer treatment uses.

The introduction to the guidance gives as the

reason for the guidance -- and it's one of several reasons, but certainly a critical reason -- that from an historical basis, there's been an evolution of clinical development so that the types of data generated and the types of indications sought are now not what they were in 1962, for example, when the clarification on effectiveness for drugs legal standard was set.

There are narrower, more closely related indications which occurs as we understand diseases better and we understand different subsets of patients and diseases. We're beginning to understand more of the genetics of diseases, and we have, in many cases, more finely focused agents that may fit better in certain stages or subsets of diseases. We have many agents that have very related similar uses in different populations, in different combinations, alone or in combination, in different doses.

Also there has been a trend from having collections of relatively smaller trials typically done at a single center to having more rigorously designed and analyzed multicenter trials, and all of these have impacted the thinking about effectiveness and particularly about numbers of clinical trials.

Now, a key focus of this document and of FDA policy is the need for independent substantiation of clinical data, and this underlies the issue of how many

clinical trials might be needed and the question of -- I'm forgetting what the word was, but the question in FDAMA -- the legal standard -- I don't want to misquote that. Hold on a second -- of confirmatory evidence, of one trial and confirmatory evidence.

This makes quite clear that what the agency is interested in is not replication, something that had been frequently used to describe the drug standard of more than one clinical trial. It's usually not wise to do the exact same trial twice. And what the agency is really looking for is evidence that substantiates the evidence that might be present in a single trial and often may come from a related trial but one that differs in ways that the document discusses.

Some of the reasons for substantiation are the possibility of systematic bias in a single study, the possibility, reflected by the p values, that the positive results might result from chance alone, issues regarding lack of generalizability if the study is done in a single trial with a single regimen and entry criteria and so forth. There are often many unanswered questions about generalizability and rarely, but sometimes present, concerns about fraud.

The general default and the focus of this document -- the general default position of the agency is

that the most common and usually best way to provide independent substantiation is to have two or more adequate and well-controlled trials, each demonstrating efficacy.

However, there are many, many exceptions to that general default position. The document starts by listing some areas in which no new efficacy trial may be required for a new indication. One is the area Dr. Weiss will be speaking about in more detail: pediatric use where pharmacokinetic data, together with safety data relevant to use in children may well bridge the gap from adult use to pediatric use if enough is known about the pathophysiology of the disease and the pharmacology of the drug.

New formulations and strengths of a drug, if there are data showing bioequivalence and pharmacokinetic linking to older formulations and strengths, may well not require additional trials.

Even new doses or regimens. If there's a very well understood pharmacokinetic and pharmacodynamic relationship, someone can predict efficacy of those new regimens.

This is a somewhat old slide. I'm not sure of the status of it now, but what internally in the agency has been called the "animal rule," which recognizes that there are some clinical settings in which clinical trials are impossible. This refers not to the many settings where we

hear, well, we can't really do that trial for this, that, or the other reason, but specifically most commonly to settings such as preventative or therapeutic treatment for, say, a disease caused by a bioterrorism vector where that disease does not commonly occur outside of that setting and it would be very hard to do a clinical trial demonstrating effectiveness. One, with animal studies, together with certain pharmacological studies, say, inducing immune responses, for example, might be able to approve a product despite the lack of the clinical investigations requirement of the law.

The effectiveness standard document then clarifies and has for each of these bullets a paragraph or a few paragraphs -- clarifies the types of independent substantiation that the agency might find acceptable other than a second study when there's a single study establishing effectiveness of a trial. And these include: evidence that different doses, regimens, or dosage forms of the product are also effective; evidence that the product is also effective in other phases of the disease; evidence that the product is effective in other populations; the issue of combination or monotherapy. A single trial showing that the drug is effective as a monotherapy supplemented by a single trial showing that it's effective in a certain combination, those two trials may substantiate

each other or either might substantiate the first.

Effectiveness in a closely related disease. As I pointed out, disease categories and indications are often being more and more narrowly defined, but if we know a product works in one disease and there's a very closely related disease or even -- as it says diseases with the same purpose of therapy -- a disease that's physiologically more different like infections in different organs in the case of an antibiotic, single studies in two different organs might suffice.

And evidence of different clinical endpoints might each support the acceptability of a claim in the other so that if you have one trial showing a drug effect, say, exercise tolerance, and another showing that it affects, say, mortality, although neither finding what's replicated in the other trial, there may well be a setting where both findings are considered supportable. Again, the standards by which this sort of inference will be acceptable are somewhat explained in somewhat more detail in the document.

The next area is an area perhaps of importance particularly to biologics, although it applies to all agents: independent substantiation of a single study by pharmacological or pathophysiological endpoints.

Now, the general tenor of this section is that

it's almost always the case that there's a rationale for why a drug works and that it has relevant pharmacology. And it's not the intent that the agency will take the fact that it has any physiological effect that seems relevant as substantiating the evidence of efficacy, but it defines parameters where that might be the case. When the pathophysiology of the disease and the mechanism of action of the drug are very well understood, but the pharmacological effect is not a validated surrogate or an acceptable endpoint for accelerated approval. There are some pharmacological effects which in their own right are already accepted, and this is a non-issue. If you lower blood pressure in hypertension, that's considered an accepted surrogate for approval.

In the case of accelerated approval, as I'll talk about a little bit later, a surrogate need not be fully validated, but needs to be reasonably likely to predict clinical benefit to be acceptable for marketing approval.

The linkage needs to be not just theoretical but based on prior therapeutic experience or well understood pathophysiology. So, there needs to be a pretty strong database to support the notion that this physiological effect will correlate with efficacy. An example given is replacement therapy. I think there's a

specific example of a clotting factor replacement. If the disease is known to be clearly due to a deficiency and there are data demonstrating both replacement of that deficiency and restoration of physiological activity, that those sort of data may well supplement a single efficacy trial and establishment of effectiveness.

There's a cautionary note of single trials with compounds with relevant pharmacological activity, such as suppressing arrhythmias or inotropic agents, which of course you may well know. In both those cases, we've observed trials where drugs were effective anti-arrhythmics or effective inotropes but, when studied in greater detail, were found to increase mortality in cardiovascular disease.

The next section of the document talks about when a single study may suffice. Generally, this will be applied to situations where there's a mortality or an irreversible morbidity effect or prevention of serious illness. And those are often situations where, in fact, it's practically or ethically unfeasible to confirm single studies, if those studies are quite compelling or convincing. In most other cases, the default position is that a single study would not suffice.

The single study should have generally some of the following characteristics. These are the characteristics that are looked at to determine its

adequacy. Being large and multicentered, having internal consistency within the study, factorialization with internal confirmation.

Factorial studies are designs which allow more than one comparison. So, you may have a placebo versus drug A by which you can look at efficacy of A, and then you might have drug B arm versus A plus B, another comparison of separate patients within the same trial, relevant to the efficacy of drug A. This pattern is in increasing usage and provides additional internal confirmation or has a potential to provide that.

Effects on multiple endpoints within the study that are not closely related to each other, and findings in a study that are statistically very persuasive. Here too, there's a caution about considering the totality of the data, noting cases where a single trial showed efficacy but other pieces of data suggested that that may not be a definitive finding, and future trials showed, in fact, that it could not be replicated.

The next section of the document, after dealing with the quantity, if you will, the number of trials needed, talks about quality of evidence and quality assurance because the standard pharmaceutical approach has been submitting detailed amounts of all data collected in a trial, together with careful monitoring and checking, 100

percent checking, of the validity of each data point. But not all trials are conducted that way, and there have been many questions about use of other types of data in the regulatory process. This document provides guidance in that regard: the first of two-part design, the use of literature reports, the use of study reprints, if you will. The second section is about the use of studies that have not been quality assured in the typical manner.

It provides guidance that I think will be more useful or mostly useful to sponsors seeking approval as to what sorts of information they might seek to obtain that would be useful in improving the value of an article which was not done perhaps under their sponsorship and for which they do not have a full data set but they have reprints. This includes availability of the clinical trial protocol and its amendments, the existence and availability of a prospective analytic plan, randomization codes and entry dates, full accounting for all subjects, a record of critical data by subject, and information particularly if safety is an issue, which it isn't always an issue because often these are drugs that have already been approved with a large safety database, information on deaths, serious adverse events, and dropouts.

The areas in which use of literature reports alone are most likely to be acceptable to the agency are

those which have multiple independent studies, detailed reports, objective endpoints subject, therefore, to problems of bias, robust results by prespecified analyses, and which were conducted in organizations with established standard operating procedures and a history of implementing those procedures for clinical trial development in an effective manner.

Then the issue of studies with non-standard QA, which means quality assurance that deviates from the typical industry approach of checking each data point, visiting all sites before, during, and after the trial, and providing a reasonably high level assurance of accuracy of the data submitted. A large number of trials in recent years have been conducted by multicenter groups, by NIH, other organizations, which take different approaches, large, simple trials, many other types of trials which often are quite acceptable to the agency in terms of the quality of data.

And the guidance provided here is that the critical factors are that there have been or be a prospective plan for quality assurance, relatively simple procedures in the trial which minimized the likelihood that they are not followed correctly, availability of primary data in the trial so that the quality can be checked when questions arise, primary data like medical records, and

that the trial have been conducted by a group with established procedures and a history of implementing them regarding quality assurance.

I'd like to take just a little bit of time, although it received more prominent billing in my title, to talk about the fast track policy.

A lot of the fast track policy really has to do with how the agency will interact with sponsors seeking to develop products for serious and life-threatening illnesses which have the potential to address unmet medical needs and really come into play largely in the developmental phase and address issues like the types of meetings and guidance that the agency will support. I'm not going to go into too much detail on that, but I am going to focus on the fast track policy to the extent that it provides some clarification regarding the effectiveness standard.

The Food and Drug Administration Act of 1997 again instructed the agency to develop guidelines regarding how we deal with products for serious and life-threatening illnesses and also presented some new authorities and some new approaches to older authorities. This provision is implemented in another document, which I've not distributed but again is available on the web site cited, entitled Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application

Review.

Now, a lot of what this document does and a lot of its purpose and a lot of Congress' and industry's purpose in asking for it was really to consolidate and clarify programs already in existence. And I wouldn't underestimate the benefit and value of that. It turns out that the affected public, including pharmaceutical sponsors, I think had relatively limited understanding of a collection of policies that have evolved over the last 10 years, in many cases in response to issues raised by patient communities, HIV, cancer, and other serious and life-threatening diseases.

But those documents were found in many places, some of them rather obscure and hard to find, preambles to regs that few people could locate. So, really one of the critical issues of this guidance is to put everything in one place. It's a road map to what the agency will do regarding treatments for serious or life-threatening conditions with the potential to address unmet medical needs.

It has some new provisions in it, some new approaches. One is designation of such products or more appropriately product development programs, products together with indications and planned development programs to achieve those indications essentially prior to filing

the IND or at the time of filing of the IND so that while the agency has always had priority designation for review of NDAs and BLAs, or at least for many years has, this now provides this sort of designation early on with impetus for the agency to provide additional support to development of those products that receive this designation.

I think an important issue is new clarifications in this document about what the agency means by a serious of life-threatening condition and particularly what the agency means by treating a serious or life-threatening condition. I won't go into detail on this point, but it talks about differences between treating the condition, treating manifestations of the condition. It addresses issues such as treating the side effects of drugs used in a serious or life-threatening condition, such as the CSFs that we see from time to time in this committee. It addresses of what this means vis-a-vis diagnostic agents and preventative agents. It provides substantial clarification and clear and, I believe, highly appropriate standards for what makes a product a priority, what are the critical features for broad varieties of products.

Similarly, it provides clarifications regarding what the agency means by potential to address an unmet medical need, what it means to have potential, what exactly is an unmet medical need in this context. The agency still

has ongoing work to further develop standards regarding how we determine what we call an unmet medical need or what we mean by the standard used elsewhere of beyond existing therapies.

Now, the part of this document that has the most relevance to the efficacy and to issues that might come before this committee, in addition to defining what's eligible, are other provisions that also pertain to the accelerated approval regulations, something that has come up from time to time in a variety of committees, often the question, well, would this product be eligible for accelerated approval as opposed to the more traditional mechanisms of approval. In addition to defining the criteria related to seriousness and so forth, this document also provides -- and I'll summarize briefly -- some clarifications regarding a provision in the accelerated approval regulations regarding accelerated approval based on clinical endpoints other than survival or morbidity. Accelerated approval is generally thought to apply to surrogate endpoints, and there was considerable congressional interest and inquiry into the implications of the application of accelerated approval to clinical endpoints.

There's also a new provision in this document, probably a fairly important one, but not one that I'll go

into detail with this committee, which allows for a company to submit an incomplete application under certain circumstances when some portions of the application are complete. Perhaps the clinical data are complete, but validation of certain aspects of manufacturing are yet complete.

To talk about what's new in the accelerated approval regulations, it's probably worth giving a brief overview of the accelerated approval regulations, something again that comes up from time to time in our deliberations.

It applies to serious or life-threatening illnesses. Another standard for its implementation is not the wording in FDAMA, "potential to address unmet medical need," but is a closely related wording, "meaningful therapeutic benefit to patients over existing treatment."

Importantly, it has a standard of adequate and well-controlled clinical trials, the same evidentiary standard that I was just talking about at some length. So, the nature of the evidence proving the point, if you will, is not different, and the quality of the evidence and the standard for the evidence is not different. This is an important point.

There was some confusion as this issue was under discussion. Would this mean, for example, that now p values of .1 are okay if it's a serious illness? The

answer to that question per this regulation and the implementation of FDAMA from the agency is, no, that is not the intent. The evidentiary standard remains the same except that it can apply to a different sort of endpoint, not simply a clinical endpoint, but the accelerated approval regulation has noted that it may also apply to the use of a surrogate endpoint that is reasonably likely to predict clinical benefit, reasonably likely being a standard substantially different from validated to predict clinical benefit. And it talks about that being based on pathophysiological, pharmacological, and other types of data.

And the regulation also has this provision which again had been under-utilized, essentially unutilized, until recently and which we've attempted to improve and increase the utilization of through clarification in the guidance document, the use of clinical endpoints other than survival or irreversible morbidity. And I'll give a little more detail on that in just a moment.

Then I think as many of you are aware, the regulation carries sections about requiring post-approval studies to confirm the effect on the clinical endpoint or ultimate outcome in the disease, the potential for certain restrictions on the use of the compound, mechanisms for

withdrawal of those compounds which fail to confirm efficacy or in which there's a failure of due diligence in pursuit of the data to confirm efficacy, certain restrictions on the promotion of such compounds, and some other issues that I won't go into detail on.

I think this is my final slide, which is good because I'm not holding up here.

The guidance document, as I said, on fast track, for which I've given you the reference, provides some clarification in some detail and this highlights a few of the issues, regarding what is intended or meant by accelerated approval with clinical endpoints. This has been a somewhat confusing issue because clinical endpoints have always been acceptable for traditional approval, whereas accelerated approval allowed surrogate endpoints to be acceptable in certain circumstances. But the agency's intent is that there are circumstances in which clinical endpoints are not and have not been in the past acceptable for approval and that this is a broadening of approaches of potential routes to approval that are clarified here.

The first one I've listed here is effects on lesser symptoms which do not per se outweigh risks but are expected to lead to a favorable effect on ultimate outcome. So, this in a sense is a surrogate. It's a clinical endpoint that is functioning as a surrogate for other more

important endpoints.

I can't speak to specific cases where I know this will be the case, but for example, you might imagine a serious disease, a type of cancer or infectious disease, characterized, say, by night sweats or weight loss where one might believe that a drug which had a profound effect on those phenomena was reasonably likely to have a profound effect on ultimate outcome because its mechanism of action was such that it wasn't directly preventing sweating, it was really treating the tumor. And one might be able to use those endpoints that are reasonably likely to predict, again not endorsing a particular endpoint, but that's the general notion, that clinical endpoints can also be used as surrogates for other more important clinical endpoints based on the same standards as non-clinical surrogates have been used under the accelerated approval regulations.

Short-term benefit in chronic conditions where short-term benefit per se does not outweigh risk and durability is expected but uncertain. Now, in most chronic diseases, the agency is going to want some evidence of some durability of benefit for chronic use and they will want some durability of safety data as well.

There have been cases where drugs have shown remarkable benefit over the period of, say, a year or so where the nature of the disease and the process and of the

treatment and of the side effects are such that if that were to wear off before three or four or five years, it might well be that there isn't a favorable risk/benefit situation. And this makes clear that rather than require three to five years of data, the agency also has an option under certain circumstances to accept one year with the presumption that efficacy will persist but with the stringent requirements of the accelerated approval regulation to require that the persistence of efficacy be, in fact, proved in the post-marketing period.

A third example would be a drug with substantial benefits that in their own right might be efficacy data suitable for approval, but where there exists significant but limited concern regarding adverse events and ultimate outcomes. So, we've seen cases of, say, cancer interventions which might have significant impact on important symptomatology, important complications of cancer, some of the agents used to prevent the toxicities of cancer therapy, but where there are variable levels of concern as to the impact of those agents and even the possibility of potentially harmful impact on ultimate outcome on cancer growth.

And this makes clear that we see a third potential approach to data in those cases where the concerns are high enough that the agent may actually have

an adverse effect on the cancer. We would likely require that to be studied in the pre-marketing period.

Where the concerns are very low and highly remote, we may well just do a standard approval with some post-marketing collection of data to ensure it's not the case.

Where the concerns are low but not so remote, we might do an accelerated approval with the stronger post-marketing commitment and potential for withdrawal depending on the ultimate outcome.

So, we believe that this regulation will give the agency and, to some extent, its advisory committees more flexibility in how we look at the appropriateness of data, its adequacy for approval -- it's not a regulation. I misspoke. This guidance will clarify ways in which the regulation might be used to accomplish those ends while still ensuring that products are safe and effective and come to market in a timely manner.

And with that, I'll close. Should I take questions now if there are any, or wait till after Dr. Weiss?

DR. SALOMON: I think we have a little extra time, Jay, so if there are some specific questions. Yes, Dr. Broudy.

DR. BROUDY: I'd just like to make the point

that we have been de facto using this process in this committee's deliberations for the five years that I've been on this committee. If you think about the approval of G-CSF or GM-CSF or a number of the biological agents, the stem cell selection devices, we have not shown that these decrease, for example, infectious death during hospitalization after leukemia induction chemotherapy or decreased death from breast cancer, for example, but we've used a surrogate endpoint such as day of neutrophil recovery. So, in fact, we've been using these guidelines in our deliberations for a number of years, and I don't see anything that's truly new about this that differs from what we've been doing over the past five years unless you have some other points you'd like to make.

DR. SIEGEL: Well, in fact, the initial approvals of those agents and some of their indications were accompanied by data demonstrating the decreased hospitalization and decreased antibiotic usage and decreased episodes of febrile neutropenia which is an endpoint which is hybrid, if you will, between a lab value and a clinical event, febrile neutropenia. And we, in fact, discussed with this committee in 1994 and 1995 which of those endpoints to use when. So, I just want to, as a record of fact, indicate that to some extent or varying degrees we're dealing with endpoints for some products that

have already been validated.

Having said that, I would have to agree entirely with your comments. For the most part, both this issue of evidence of effective and these issues of acceptability of different types of endpoints clarify rather than change approaches the agency has been using.

There are some subtle changes, and in fact I think that one of the things that they accomplish is to provide consistency within the agency so that there have been different approaches at use within the agency. It's my belief and our belief that the approaches that we've harmonized on are largely the approaches that have been utilized by my office and this committee. So, we may be seeing less change than certain other areas, but we're providing additional and I think important clarification to our reviewers, to sponsors, to the committee.

There are some things that are more specifically new here. I tried to highlight those and some options that are new.

DR. SALOMON: Dr. Auchincloss?

DR. AUCHINCLOSS: Jay, can you just clarify for me what's the difference or the relationship between these various guidances which include the fast track guidance and the accelerated approval reg?

DR. SIEGEL: Are you asking what's the

difference between regs and guidances in general or how they relate to each other?

DR. AUCHINCLOSS: Is the regulation the basis for the guidance or are they separate things?

DR. SIEGEL: Yes. A regulation is something that's legally enforceable and that is a way that a government agency implements its legal mandate. A guidance document is used as a way to provide guidance as to, amongst other things, how best to be in conformance with regulations. Guidance documents clearly and always are a proposed approach. However, alternative approaches, if justified, as ways of meeting a regulatory standard or regulation, can be also be deemed and found to be acceptable.

So, in the specific case, therefore, of the specific question you're asking, the accelerated approval regulation and other regulations implemented under the Food and Drug Administration Modernization Act, the Food, Drug and Cosmetic Act, and the Public Health Service Act establish the standards for efficacy, the standards by which we can approve products, and in the case of accelerated approval regulation, the standard for accelerated approval.

However, we found, for example, with that guidance that there was a lot of confusion and sometimes

inconsistency as to what was serious and life-threatening. There was some general public thought that that really only meant AIDS or only AIDS and cancer, for example. There was some confusion as to what the use of a clinical endpoint for accelerated approval would be when a clinical endpoint should get regular approval. So, a guidance document is an important document that provides clarification and guidance but doesn't have that sort of regulatory impact.

DR. SALOMON: Dr. Champlin?

DR. CHAMPLIN: The guidelines that you've proposed are largely directed to making sure there's a high level of confidence that a product is, in fact, safe and effective for its approval.

My concern is, as the process becomes increasingly onerous and expensive, particularly small market or orphan indications then don't seem to be economically feasible for companies and corporations to develop. As the understanding of medicine advances, we are increasingly splitting disease states into smaller and smaller entities defined by their pathophysiologic mechanisms. So, you're increasingly developing these sort of small potential indications for therapeutic intervention.

So, the bottom line is that the guidelines should ideally be a balance that would favor and enhance

and encourage the development of new and effective treatments. Right now, at least, there's a perception that the guidelines or at least the regulatory process is an expensive and onerous one that only justifies development of a $100 million drug. So, somehow we have to come to, again, a balance of those opposing considerations.

DR. SIEGEL: I would only comment that your phrase "as the standards become more onerous, we run into these problems," that these documents to a large part and the act itself to a large part represent making standards less onerous. I'm not specifically addressing whether or not they're too onerous, which is the point that you're raising, as I think you have legitimate concerns that, of course, also need to be balanced against the importance of having adequate safety and efficacy data.

But it should be noted that this evidence of effective document, for example, represents a significant move from, in many parts of the agency, routinely requiring more than one clinical trial to a clarification that there are many cases in which one clinical trial will suffice and, in the case of fast track, to providing clarification regarding a broadening of the types of endpoints that might be acceptable for approval and types of approaches.

On the issue of orphan indications, of course, I haven't addressed those, but there are in place a

substantial amount of laws and policies to try to assist and facilitate development of products for orphan indications. Interestingly, many of the products that this committee sees have been developed under orphan drug provisions, which is not to say necessarily that what we have is currently adequate or that there might not be other ways to improve the process, but just to note that there are a lot of relevant provisions.

DR. SALOMON: Dr. Sausville?

DR. SAUSVILLE: I have a question or a comment and it relates to this use of surrogates and clinical endpoints. How does the agency impute value to different types of surrogates? Because I think it's one thing to say that you're going to use surrogate markers or clinical endpoints. But I think there's a lot of confusion certainly among sponsors in terms of when they come to us and talk about the strategies they might conceivably use for an investigational agent, and there may actually be confusion in the clinical community as to what surrogates to use because ultimately not all surrogates are created equal I guess. So, I'd be interested in your thinking on that.

Also the comment would be I'm concerned that tying the, quote/unquote, effects on lesser symptoms to some expected ultimate outcome could potentially not

address clinical needs. And to pursue your example, let's say that you had a drug that was really good for night sweats but didn't actually treat the underlying cancer. I imagine most people who were in the unfortunate position of being afflicted with that problem would rather not be sweating even if their survival was not affected. How would you address that?

DR. SIEGEL: Fair enough. Let me address both parts of those questions.

I think the first part is a critical question of our times. The Food and Drug Administration Modernization Act of 1997, in fact, instructed not the FDA but the Department of Health and Human Services to address the issue of utility of surrogate endpoints, and in part as a result of that legislation, but also other perceived needs, as you're quite aware, there have been two NIH/FDA co-sponsored conferences, one this past April on biomarkers and surrogate endpoints in clinical diseases, one I guess it was October or November on issues regarding statistical and clinical approaches to the validation of surrogates.

I wouldn't really be able to answer your question as to how exactly we determine acceptability of an endpoint, because it's too complex and dependent on the specifics of a given case, except to say that we believe the best time and way to do that is prior to the conduct of

the definitive clinical trials. We're quite open in these settings to meeting with sponsors and encourage that to discuss the acceptability of the surrogate.

And we also believe that there's a role for advisory committees on critical questions that arise in that area, and it would be our intent and practice to invite either individual members of advisory committees with appropriate expertise to discussions with the sponsor or, in some cases, to come to an advisory committee, as we've done in a number of cases in the past specifically to talk about acceptability of different endpoints in different diseases.

DR. SALOMON: Yes. In fact, I wanted to interject. I think that that's probably one of several of the major roles expert advisory committees such as this one play. I have to say over the last seven, eight years that I've been participating in various ways with these committees, we've had just that, meetings where specifically we dealt in a number of different areas with the surrogate endpoints. Because your point is well taken, not all surrogate endpoints are the same.

What's more concerning to me is sometimes our best clinical judgment on the value of the surrogate endpoint halfway through a trial suddenly becomes very clear that that surrogate endpoint has a lot less meaning

than it had when we originally made our projections.

DR. SIEGEL: Yes. The question is also a very important one. You asked about the clinical endpoints. It's a little clearer, I hope, in the document than I presented. But on that case, for example, of night sweats -- and this is the confusion because clinical endpoints are in fact acceptable for approval in their own right.

What the issue boils down to is what is the collection of benefits that you're going to weigh against risks. So, if you had, say, an entirely safe agent that prevented night sweats and did nothing else, that would be an approvable agent.

Now, if you had a cancer therapy that caused, say, profound neutropenia and intestinal ulceration, and your evidence of efficacy was based largely on night sweats, but you could establish that that impact on night sweats was reasonably likely to predict favorable impact on an ultimate outcome of survival or other more important -- well, the benefit on night sweats per se might not weigh adequately against the risks of the drug, but the night sweats might be taken as a surrogate for a greater benefit that we might consider under accelerated approval. So, that's the difference. In fact, that sort of setting is not infrequently seen. And in that regard, then the night sweats become more like a surrogate because in their own

right they wouldn't merit approval because of the toxicity of the drug.

DR. SALOMON: Jay, one of the things you didn't mention -- and I didn't have a chance to review the document -- is where do the results of international trials come in in this approval process. It has been an issue in the past and I know the FDA has a position on it.

DR. SIEGEL: Oh, yes. Through the ICH process, the International Conference on Harmonization, we've been quite involved, and I personally have been very involved, in international negotiations regarding a variety of issues of international standards, including specifically the acceptability of foreign data.

The current position is that foreign clinical trials that are adequately and well-controlled and conducted under good clinical practices can provide a substantial part of the data in an application, in some cases, the entirety of the application, with the provisos that there are often specific concerns regarding the fact that concomitant therapy may differ, that diagnostic methods may differ in regions of the world so that different stages of disease may be treated or assessed differently and other factors.

And so, what this guidance document, the ICH E5 guidance on ethnic factors and the acceptability of foreign

data, does is define sets of intrinsic factors, genetic factors such as liver, metabolic enzymes, and extrinsic factors such as diet and medical practice issues that might impact drug efficacy and provides guidance as to how those factors should be assessed and where they may then call for a strategy of bridging data so that in some cases foreign data in their own case might suffice. In some cases, foreign data with certain bridging data to show that they are applicable in the U.S. or the home region will suffice. In some other cases, trials may be required in the U.S. But that does not exist as a regulatory standard, and we are quite open to the use of foreign data.

DR. SALOMON: Dr. Auchincloss.

DR. AUCHINCLOSS: Jay, just a clarification about how I should be listening to this presentation and Karen's in just a moment. I found the update on FDA policy very helpful to me, but I'm not sure what you want of us, the committee. I don't see questions for us. Is there some input that you want us to be thinking about?

DR. SIEGEL: This was done as an update not seeking input, which isn't to say that input isn't -- you know --

(Laughter.)

DR. AUCHINCLOSS: No, no. I understand.

DR. SIEGEL: -- isn't welcome.

(Laughter.)

DR. SIEGEL: It's just to say, no, I'm not specifically seeking input.

DR. AUCHINCLOSS: Not encouraged.

(Laughter.)

DR. SALOMON: Dr. Miller.

DR. MILLER: Do you have any data on how this has been implemented, the percentage of drugs that have applied for fast track or biologics that have applied for fast track and have been granted a fast track? And are there any drugs that have gone through the fast track process? I don't think we've had any biologics that have actually been approved.

DR. SIEGEL: Well, Betty, do you have those data? Betty Goldman, who is my Associate Director for Policy, kind of chaired the FDA's policy implementing fast track guidance and may have some information on that.

MS. GOLDMAN: I don't have the numbers with me. I'd say a couple of months ago, I think at the end of April, approximately 80 applications for fast track in both CDER and CBER, Center for Drugs and Center for Biologics. I think about a third had not been designated, were actually turned down for designation, and we've had a couple go through the rolling review, the incomplete application process.

MS. MEYERS: Two-thirds then have been designated as fast track?

MS. GOLDMAN: Of those that have applied. Of course, it is completely up to the sponsors whether to apply or not. We don't solicit the applications. Of those that applied, I would say approximately two-thirds have been granted.

MS. MEYERS: About two-thirds have been. Yes, it seems to me, because I track new drug approvals every month, that there are an awful lot of me-too drugs that are being designated as high priority. For instance, the new class of arthritis drugs, for example, even though there are three or four of them, have all been high priority, and I just don't understand it.

DR. SIEGEL: Yes. Let me clarify a few things. First of all, we're talking about a number of different things here. Fast track designation is something that usually occurs not at the approval or priority stage, but is something that occurs in most cases relatively early in development and is something that kicks in then additional meetings and support in terms of planning the development of a drug even before it has gone into humans.

And the reason some get rejected is largely because the plan for the development may not really address the issues that fast track was intended to address. Will

this product truly be studied for its potential to treat something serious and will it be studied for its potential to address unmet medical needs? And we specifically exclude me-too type drugs or even drugs that at the end you won't know if they're me-too or not or if they offer something new from that designation. So, the policy is intended to limit to those drugs whose developmental program will really establish an important role for the drug or establish whether that exists.

As to the approval issue, I can't speak specifically -- I guess you're referring to the Cox II drugs. Those are over in the Center for Drugs. It is the intent of the priority designation for review as implemented in Biologics and I believe also in Drugs, although they have a somewhat different standard there, that that not be applied to me-too drugs.

There is another guidance document -- you'll find it on the same web site -- as to how each of the centers applies its standard of priority designation. It came out sometime last year. The language is in there regarding the requirement that the drug offer something new and different.

If it's your perception that you don't understand why that's applied or you believe it may have been applied incorrectly, you might want to inquire.

Robert DeLap is the office director I know, a good friend of mine, who is responsible for the arthritis drugs and will probably be able to provide some guidance as to that issue.

MS. MEYERS: If three companies come to you with the same drug and they all ask for priority review, even though it's the same drug, you might grant priority review to all three --

DR. SIEGEL: Well, what's the same and what's different is a very complex issue. This committee actually -- I think it was to this committee that we brought two drugs actually, Simulect and Zenapax, which were two drugs for organ transplantation, antibodies to the IL-2 receptor. Or at least we brought one of them. Do you remember? Did we bring both of them? We brought one of them, yes. And that came in at around the same time. These are complex.

The simple answer is that if there's a drug approved for an indication and another drug has not shown that it does anything beyond being an alternative that is not a priority. And in fact, there are specific examples of cases that I can think of in house now where we've made that very clear where one drug got approved as a priority; a few months later, the other drug comes in and is not a priority.

Now, if a drug comes in at a time when a

competitor drug is under review, well, there's still an open question as to whether that drug is even going to be approved, and so in fact, it may well get priority designation.

And then we face the question, well, if we're halfway through the review, do we change the designation and what does it mean to change the designation in the middle of the review if we've already proceeded on a priority time line. And we don't really have a clear answer to that question, and often we don't change it, though.

MS. MEYERS: Is it a significant strain on the FDA staff that two-thirds of your biologics are designated as priority drugs?

DR. SIEGEL: I think it's more than two-thirds, and the answer is yes. It's a tremendous strain.

DR. SCHWIETERMAN: I think it's an excellent question. I think it's important to keep in mind that the fast track approvals depend not simply on whether the agent is similar to the other agents but, as Jay was pointing out, the indication. So, you can have actually a class of drugs, all of which work relatively similarly with respect to their physiological mechanisms, but the sponsor is pursuing different aspects of that disease.

One of the virtues, frankly, of fast track is

that it encourages sponsors to seek out new ways. An example: if you give an anti-TNF for the treatment of signs and symptoms of Crohn's disease but then you have another company that comes out with maybe another agent and they seek it for steroid sparing of that same disease, they would get fast track designation even though they have almost virtually the same agent, these sorts of things.

I think that that was one of the intentions of the fast track document. I think that that we think that that's actually a good thing because it gets sponsors to -- and of course, we make them address that particular concern.

So, maybe that helps clarify some of your questions.

MS. MEYERS: In other words, it's encouraging innovation?

DR. SIEGEL: It's encouraging getting better and additional and more important clinical data in the sense that a drug of the same class, if there's already a drug approved that has a certain symptomatic indication and a competitor with a drug that is similar and might have a similar use but claims to show a survival advantage or some other -- our tendency would be to give that a priority in part because it might be a superior drug. But even if we think that the other drug might also have that effect, it

does in fact encourage sponsors to do trials which provide important and useful clinical information, such as impact of a drug on survival.

DR. STEIN: I don't want to prolong the discussion, but I want to answer Dr. Miller's question about fast track approvals for biologics. Actually the agency's first fast track approval was a biologic. It's Herceptin, a monoclonal antibody to the HER-2/neu receptor, and that was approved in September of 1998.

DR. SIEGEL: Yes. That was the first approval of a product with designation. Right.

MS. GOLDMAN: I just want to clarify that two-thirds of the products that have applied for fast track designation received it. They're usually very on in development, often before they've done any clinical trials whatsoever. So, it's based on animal preclinical information or whatever. So, just as most drugs don't actually make it through to an NDA or BLA application to begin with, they have a long way to go in showing they continue to meet the potential to address an unmet medical need. That two-thirds shouldn't be linked to the two-thirds then going to priority review later on.

DR. SIEGEL: I clearly made a mistake in devoting only three or four slides to fast track and only focusing on effectiveness because I think I may have

created more confusion than I clarified.

But just as an issue of background so you'll understand it, the fast track is an aggregation, if you will, of a large number of policies that have to do with serious and life-threatening illnesses. So, there's early designation at the IND phase. This is something that's new. That triggers whole bunches of meetings and support and so forth, some of which already exist and defined under subpart (e) regulations promulgated 10 years ago. The program incorporates but does not automatically trigger the potential to use the accelerated approval regulation for approval based on a surrogate. It incorporates and probably does essentially trigger the priority review mechanism. If you're a fast track drug and you proved what you intended to prove, you should meet the standards for priority review. And it enables and the fast track designation is required for but is not the sole requirement for the ability to submit incomplete portions of an application. And there are other things involved as well.

So, when we talk about fast track, we're talking about a whole collection of policies, all described in one guidance as to efforts the agency is making to facilitate development of treatments for serious and life-threatening illnesses that add to the therapeutic armamentarium in significant ways. But priority

designation, accelerated approval, IND fast track designation are amongst those programs. So, sometimes people have referred to those as fast track. There's a little bit of terminology confusion, but that's basically the nature of what fast track is.

DR. SALOMON: Two more comments. Dr. Sausville?

DR. SAUSVILLE: Maybe the program is too young, but what fraction of agents that either have been approved or are in the process of being approved by fast track that lose that designation owing to clarification of things in development?

I mean, everyone would praise moving forward with things rapidly. On the other hand, one doesn't want to create the impression that there are ways of getting around or parallel tracks or different tracks or depending on how you couch things, that you might be able to go this route as opposed to others.

DR. SIEGEL: Well, there's no question that over the course of the development of a drug what was an unmet medical need may no longer be an unmet medical need, and what appeared to be the potential to address that need -- the drug may no longer show that potential.

It's too early to say how often that will happen. And the agency has provided some but not complete

clarification as to whether and when it will actually withdraw fast track designation, something that has yet to happen. But what would clearly happen is if those things didn't exist, as you went through development, if you no longer appeared to kick in the criteria necessary for, say, accelerated approval based on a surrogate because there was already an approved treatment for that indication or if you didn't kick in the criteria for a rolling application or a priority review, you might not get that even though you had initially received fast track designation. Whether or not you would get a letter of de-designation is something that's not yet clear.

DR. SAUSVILLE: I just think that the criteria for such a letter and the process used to make that determination needs to be pretty clear to people so that they're aware.

DR. SIEGEL: There are proposals out there. We're receiving public comment on it. Obviously, there are significant implications that are of some concern to sponsors as to what it means to get a letter that says you've been de-designated and so forth.

(Laughter.)

DR. SAUSVILLE: You're done.

(Laughter.)

DR. SIEGEL: And we're aware of that and

working on that issue.

DR. SALOMON: Dr. Vose?

DR. VOSE: I just had one short comment I want to make. I want to kind of put a plug in for having the appropriate clinical and scientific expertise on the committee to try and deal with not only the biologic aspects but also the aspects of the specific disease that we're dealing with and also to have those people or other people involved in a lot of these early meetings that you're having because I think they put a neutral perspective on. They're not involved with the drug and they're not involved with the FDA, but the expert can be helpful as far as the overall picture in helping with some of those, kind of standing up for the patients and what's needed in that disease entity. And I think the ones at least I've been involved with have been kind of helpful in that situation, and trying to get involved very early I think is very important.

DR. SIEGEL: Well, thank you. I think we should be doing more of that. I think that would be wise.

For the sake of the new members of the committee who may not have experienced this, it's hard obviously and it's impossible on this committee to retain all the types of clinical expertise pertinent to the products that we might face. And so, we may well take a

treatment for, say, arthritis or Crohn's disease or cardiovascular disease to a different advisory committee that has more of that appropriate expertise.

Nonetheless, we find that there are certain common themes that arise with our products such as immunogenicity that we're going to discuss today so that we have a very common practice of asking members of this committee -- Dr. Vose, I know you've done this on several occasions -- to sit as members and panelists on other committees when we take a product. We will invariably ask at least one and often several members with the most relevant expertise on this committee to sit with the Oncological Drugs Committee or the Rheumatoid Arthritis Committee or whatever it might be to discuss our products. We very much appreciate that contribution because there is a broad mix of types of issues that comes up and we struggle within the rules we operate under to bring together the right expertise so we can get the best advice on any given product.

DR. SALOMON: Thank you very much. It was very informative.

The next speaker is Dr. Karen Weiss, and she's going to address the pediatric rule.

DR. WEISS: Good morning, everybody. I am trusting that all the questions that you asked Dr. Siegel

means that there are going to be fewer for me, especially because everybody is going to want to go to the break.

But it is a pleasure to be here this morning to provide you with an update on what has been happening in the area of pediatric regulations. This has been a very active, dynamic area in the agency in the last few years. Our former Commissioner, who was a pediatrician from Hopkins before he came to the agency, had certainly a very great interest in pursuing and promoting adequate studies in pediatrics. Also the American Academy of Pediatrics has been a tireless advocate in this area. And it has culminated in a number of important developments in the last few years that I'm going to go over.

First of all, this is just some general principles that are actually set forth in one of the ICH documents. It's actually E7 which is a guidance document on Studies in Support of Special Populations: Geriatrics. But it's very applicable to what I'm going to what I'm going to be saying about pediatrics, as well other groups. And those principles are: Drugs should be studied in all age groups for which they will have significant utility, and that patients entering clinical studies should be reasonably representative of the population that will be later treated by the drug.

I think those are good principles, and I don't

think that was really apparent a couple decades ago. There seemed to be a systematic exclusion of particularly important groups such as pediatrics, such as geriatrics, such as women of childbearing potential, and over the last 20 years, there has been a shift towards more inclusion and representative of these important groups and others as well.

In order to come to the present regulations for pediatrics, I thought it would be helpful to first go through a very brief history of what has been happening in the world of pediatric regulations, and it's fairly short and fairly brief. It's 1979, 1994, and now 1998.

In 1979, that particular regulation -- and I have the citation in the Federal Register for you on all these three -- the purpose of that was to establish a pediatric use section of the labeling. Prior to that time, there was no requirement in our labeling regulations that there be any mention, acknowledgement, whatever of pediatric use of a particular drug/biologic that would be approved. So, this established it for the first time.

I will go over these all in a little bit more detail.

In 1994, it was to try to clarify certain situations, similar to the effectiveness standard that Jay Siegel mentioned earlier, where one could perhaps

extrapolate efficacy from trials in adults down to pediatric patients.

And then 1998, which is going to be bigger focus of my presentation.

So, 1979, in the regulation what was set forth, the goal of which to try to ensure that labeling of approved products would regularly contain adequate information about prescription drugs in pediatric populations. As I said, it established for the first time the particular section in the labeling called the pediatric use section that was supposed to be filled out with correct information about pediatric use.

The regulation further went on to say that the basis for the information in the pediatric use section of our labeling should be substantial evidence, the same standard that we have, from adequate and well-controlled studies in the pediatric population unless that requirement was waived.

The problem was that this regulation in 1979 did not have the effect it was intended to have. There was a pediatric use section of the labeling that was routinely put into our labels, but it really did not contain particularly useful information about pediatric use. And the reason why is because there was a mistaken impression that the only way to get pediatric claims, pediatric use

sections into the label was to conduct adequate and well-controlled studies in the pediatric population, pretty much what the regulations said. And there was that waiver clause, and the waiver was intended when other information could suffice.

However, the particular conditions for when a waiver should be requested was not very clear. I don't know if there were any cases where anybody actually asked for a waiver, and I don't think the agency really had a particularly good idea of what conditions it would follow, what criteria to basically grant a waiver.

And so the default position is what we generally had had, which was that prescription drugs continue to lack information on pediatric use. That section of the regulations that was required to be filled out basically contained the standard clause which anybody who is in pediatrics who has ever looked at labeling to try to prescribe a particular drug for a pediatric patient would see the particular statement that would say safety and effectiveness below the age of X have not been established, whether it's 6, 2, 12, 16. Whatever age they had, there was always this particular default position that was available on the labeling which was not particularly helpful because in practice, again anybody who had been in pediatrics would know, you really couldn't use the label to

help you, to guide you in terms of prescribing a particular medication for pediatrics. You didn't really know what dose to use. People would just take the dose that was recommended for use in adults and kind of do some calculation by whatever voodoo they knew about and come up with a dose for a pediatric patient or they'd take the tablets and they'd cut them in little pieces and it was never quite standard. It was very much a problem.

So, along came 1994, something that was referred to commonly as the 1994 rule. That one said, gee, 1979 really wasn't very helpful. It didn't get the desired effect. There really needs to be more encouragement of pediatric studies. There is certainly a lot of resistance to putting pediatric patients on clinical trials, which you can understand. There are issues about consent, some of the ethics. If you're going to be doing a placebo-controlled trial, is that really something you really want to do in a pediatric patient who really doesn't understand particularly the potentially painful procedures if you have to do blood drawing, when you have pediatric patients on trials who may not really understand. So, that was really I think probably the bulk of the reason not to put pediatric patients on trials.

Now, where I and many other people come from, which is the pediatric oncology side of things, that was

clearly not the case. Pediatric patients were routinely put onto clinical studies. But I think for the vast majority of many of the other products, that really was not the case.

So, in 1994, the final regulations that were proposed in 1992 and finalized in 1994 stated that there are times when you don't really have to do the complete randomized controlled trials that everybody thinks one needs to have. In fact, there may be cases where one could extrapolate efficacy from adult populations from adult data, from adequate and well-controlled trials in adult studies, and those cases would be when there is substantial evidence can include studies conducted in adults "when the agency concludes that the course of the disease and the drug's effects are sufficiently similar to permit extrapolation." In those types of cases, generally pharmacokinetic and additional safety data would be required. It said "where needed."

And you could understand that, for instance, if you were extrapolating efficacy down from adult studies to adolescents, you may not need a lot of additional information on pharmacokinetics, but if you were going to try to extrapolate efficacy from adults down to the same condition in a neonate, you might very, very well need a lot of good pharmacokinetic data to understand the dosing

because the metabolic pathways may be very, very different.

As this committee probably knows very well, since 1994 -- and actually it's about the time when this committee first formulated -- we have been asking this committee this very question. With many, many products that we have taken to this committee, data were based on adequate and well-controlled trials in adults, oftentimes with some smaller amount of data, primarily pharmacokinetics, in pediatric patients. And we almost routinely ask this particular committee, can we extrapolate efficacy? Is the disease course similar enough that we can actually do away with the controlled clinical trials in pediatrics and extrapolate efficacy from adults so that we can actually put this into the labeling?

And that has been a source of a lot of discussions. I know Ms. Meyers was instrumental in a lot of those discussions, a lot of other people here on this very topic. I think it has been very good. It's a very difficult issue to determine, whether or not you can extrapolate efficacy, and there are cases when it's probably very easy to do and other cases where it's much more difficult.

The 1994 rule basically called upon sponsors of these licensed products or approved drugs to go back and review existing data because there was the feeling that

there may already be substantial use in the community of these approved products and that in fact it wouldn't be terribly onerous. Our manufacturers could go back and gather what data had already been done in pediatrics, submit those data to the agency, and there would be a number of supplements coming in that would fulfill this particular requirement to add the appropriate information onto the labeling.

Now, the rule specifically did not require sponsors to go forth and conduct studies either for already marketed products or for new products coming on to the market. It specifically said that our sponsors should not propose labeling if they do not believe that the disease and the drug effects are similar or if pediatric use not otherwise adequately supported. So, there was no specific requirement to do studies.

The 1994 regulation was very helpful, though, because it forced all of us to really focus more on pediatrics and to think more about it, to regularly discuss pediatric studies and pediatric use with our sponsors who are coming through in development and again to bring it up to committees like this committee on a routine basis. So, it did accomplish some things.

However, in the years after this regulation issued, there was growing concern by advocacy groups, a

number of other groups that this particular regulation just did not go far enough, that there just wasn't enough data being collected, there were just not enough studies being done. In fact, when one went back and reviewed the approvals, primarily on the drug side, because that's where it's really much more of an issue, and did surveys from 1991 on through 1997 where applications were coming to the agency for an indication that had potential usefulness in pediatrics, only at best 30 percent or so of those actually contained pediatric information. So, even though it was better than nothing, it still had a long way to go and it wasn't as complete as it should be.

So, in 1997, in response to this growing concern that 1994 regulations just were not adequate, the agency proposed regulations in 1997. These became finalized in December of 1998. The title of this regulation is called Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients. It's a requirement. It's the first time now that we are actually requiring these data to be generated. This regulation became effective six months after the date it was finalized; so April 1st of 1999 it became effective.

However, even though it became effective April 1st, any new application coming before the agency from

April 1st for actually the next couple years probably will not have the data in hand at the time the application is submitted because, of course, it takes time to generate clinical data. It may take even more time to generate data in pediatric patients. Therefore, it's not going to be until 20 months after the effective date of the rule, which basically means December of 2000, when those data will have to be in hand. Obviously, we'll take it sooner if those data are available sooner, but it's not going to be until December of 2000 that those have to come in.

Let me just step back just a second and just say that in 1997 when this regulation was first proposed, it created quite a bit of controversy. There was a big dichotomy, if you will, of opinion with the proposed regulation. There were on one hand the advocacy groups who said this regulation doesn't go far enough. It really needs to be much more compelling, much more straightforward in telling sponsors that they have to get these data. There should be no exceptions, et cetera. And on the other hand, there were industry representatives, not all of course, who basically felt that the regulation had gone too far and that, in fact, FDA was overstepping its bounds. It was going to create all sorts of problems. Pediatric patients would be put on studies before it was safe to put them on studies. It was going to delay approval of

therapies for adults. These were all things that were voiced as concerns. And so, there's quite a dichotomy of opinion about the 1997 proposal.

However, despite the fact that there was this big dichotomy, one was able to, I think, try to come up with some reasonable compromises, and the regulation was finalized in 1998. And so, highlights of this 1998 regulation are as follows.

There's the presumption that manufacturers will assess drugs and biologics in pediatric patients, and that assessment should be available during development so that at the time the application is submitted to the agency, those data will be in hand, and if not at the time the application is submitted, sometime soon thereafter. What we're talking about are new indications for sure, but even other things, new dosage forms, which isn't so much an issue in biologics. The majority of our products are parenterally administered. But in drugs there are tablets, liquids, suspensions, sustained release, all those different types of formulations, and if something new comes along that might have potential usefulness in pediatric patients, that would need to be studied, a new route of administration, et cetera. So, all new aspects of a particular product, whether it's a brand new application or a new indication, et cetera, or new variation, the

presumption is going to be that those data will be in hand for pediatric patients and that new drug biologics will contain adequate labeling, as I said, at the time of approval or very soon thereafter.

The agency does have the authority to go back and require studies on already marketed products, and I'll mention that standard or that criteria in a minute.

Specifically what is not applicable in this regulation are orphan drug products, the idea being that there should be an incentive to get things on the market for orphan indications and that this regulation was not going to go further and require -- you can imagine if it's an orphan indication for an adult, it's probably going to be even much more orphan for a pediatric population. So, orphan products are excluded from this particular regulation.

So, what are the conditions where the agency will require studies in pediatric patients? One is when it's likely to be commonly used in the pediatric population.

What does "commonly used" mean? With the proposed regulation, we were taking the criteria that are used for orphan drugs, which is if it affects 200,000 or less, it's an orphan indication. However, the pediatric population doesn't make up the entire universe of the

population. It's only a fraction of it. And so, there were some manipulations that went around and some mathematics, and what came out in the final regulation was commonly used would be if it was greater than 50,000 in the overall pediatric population or 15,000 in any particular subgroup. And I'll mention a little bit later on about the different age groups of pediatrics to give you an idea. So, that was the numbers that were proposed.

So, that's one, if it's commonly used.

The second is if it provides a meaningful therapeutic benefit, MTB, to pediatric patients over existing therapies. It's somewhat similar to what Dr. Siegel already proposed or mentioned with fast track and accelerated approval, et cetera, a somewhat similar concept. So, it could be used in a very small number of patients but still provide a meaningful therapeutic benefit.

And I put this down because this was well highlighted in the pediatric regulations, and it's not mentioned many other places. In some classes of some diseases, there is really a need for alternative therapies even if it has not been demonstrated to show a particular advantage. But you can imagine in AIDS and cancer there's rapid development of resistance, and those are particular diseases where one might not have to show that it can only

be used in people for third line, fourth line, fifth line therapy, but it's a particular class where it would be important to have available therapies and alternatives for patients. So, those would also be considered to be drugs or biologics that would offer a meaningful therapeutic benefit.

And then for marketed products, a similar standard, it's commonly used or offers a meaningful therapeutic benefit, and -- it's an "and" -- absence of labeling could pose significant risk. It's felt that this particular requirement to go back and require studies on marketed products would not be used, imposed very often, maybe a few times a year. It's going to be a little bit difficult I think to determine whether or not absence of labeling could pose a significant risk, but that would be the criteria that would be used.

Types of studies that the agency will require is very variable. Just like in 1994, the agency said there are times when one may not need to do full-fledged, randomized efficacy trials, sometimes PK studies, safety studies may suffice, the same goes in 1998, a range of particular types of trial designs are available and can be appropriate depending on the situation. It can range anywhere from smaller studies of just some PK again to randomized controlled efficacy trials.

The particular age ranges that should be studied is going to depend on what ages are affected by the particular disease. In 1994, the regulations basically set forth four different age ranges of pediatric patients: neonates, infants, children, and adolescents. This is why I try not to talk about this proposal as being children, but pediatric patients because children refers to a particular group age 2 to 12, even though they're all children. In particular, these adolescent groups are.

But anyway, in the 1998 regulations, we didn't specify particular age ranges with these particular cutoff dates because we realize it's somewhat arbitrary and there may be physiological differences why other particular age groups should be studied as opposed to these definitely prescribed ones.

Most importantly, the kinds of data and studies that will be required will be only for the indication that is being claimed. If something is about to be approved or already approved for an adult indication and there's substantial off-label use in pediatrics for a different indication, the agency does not have the authority. It will not be able to ask for studies in that off-label indication. So, it's only for the indication being sought.

When to conduct studies is a very open question and one that has been the subject and will continue to be

the subject of great debate because one doesn't want to go into pediatric patients too soon. However, one doesn't want to have the default that we've had over the last couple decades, which is to be too late and in fact to not do these things at all.

So, it's going to depend on the seriousness of the disease, whatever preliminary data are available in adults, if appropriate. There are some settings where adult data are not appropriate and not necessary to have and these new products go right into pediatric populations, but that isn't always the case.

And availability of other therapies for the particular condition. In general, the regulation says this I think quite clearly. One would think about going earlier into pediatric patients if you're talking about a very serious disease where there are very few or no alternative therapies, perhaps later for things that are considered to be me-too type of products. In some cases, one might not even want to go into pediatric populations until there's substantial post-marketing safety experience that's obtained in adults. It's really going to depend on the particular situation.

Now, the regulation says that pediatric data will be available unless that requirement is waived or deferred. So, when do we waive the requirement? And it

can be waived for the entire pediatric population or for some populations like it can be required for adolescents and children but not infants and neonates for instance. So, it would be waived if it's not an advance, unlikely to be used, or ineffective in those particular populations, studies are impractical, too small. The population is geographically dispersed and it's just absolutely impossible to conduct a trial.

And then this last one, which has also been the subject of quite a bit of controversy, again not for us in biologics because we don't deal much with formulations. We don't have to think much about taking a tablet or a sustained release or a capsule and figuring out how to make a liquid formulation that's palatable. Palatable, the big thing, of course. If anybody has ever tried to get a liquid down the throat of a child, it's easier to do it for your dog than it is for your child.

(Laughter.)

DR. WEISS: So, the inability to develop the pediatric formulation. So, I don't probably have all the appreciation for all the chemistry that goes into formulations, but when this initial proposal came out, one of the controversies was the advocacy groups said that should never be a reason to waive the requirement. They should just be required to develop a formulation, no ifs,

ands, and buts. And others on the other side saying this is extremely difficult, extremely expensive, and sometimes just not feasible to do. So, if the company has, in good faith, attempted and failed to develop a pediatric formulation, they will be waived of the requirement.

Deferral. It's not a waiver, but deferring the studies until sometime later on can be available where the adult safety or efficacy data are needed to be collected before appropriate studies in pediatric patients. Of course, then the pediatric studies will be delayed.

If the product is ready for approval in adults but the pediatric studies are underway and have not yet completed, the agency has said over and over again that we would not delay approval of an important therapy that's ready to go out there for adults while waiting for the pediatric studies to be completed.

However, if there is a deferral, one would have to reach agreements -- we would all reach agreements -- regarding the timing of the pediatric data, when we would expect it to come in to the agency. And the regulation says that the pediatric studies of sponsors is going to be required to update the agency on the progress of the pediatric studies in their annual reports to the licensing applications.

One of the good aspects of this 1998

regulation, just like in 1994, was that it's forcing all of us to focus in on pediatric development early on in the development process of the particular product. The regulation specifically calls for early discussions with the agency on the need for pediatric studies and the timing of pediatric studies and the type of pediatric studies that will be required.

Specifically, if we haven't had these discussions and determined earlier on by the end of phase II development -- and actually it will be phase I for a serious or life-threatening disease, but certainly by the end of phase II for the ordinary types of products, most of which we don't have in biologics -- we tend to have the serious, life-threatening kind -- we're supposed to inform sponsors about whether or not the need to have pediatric data and when we think it would need to come in, et cetera. When we have meetings with our sponsors at the end of phase II to discuss the phase III trials and the entire development plan, the sponsors are supposed to submit in their meeting packets their proposals and their plans for pediatric studies at that particular time, if not before. And that is specifically called for in the regulations.

This is called my carrots and sticks approach. What are the incentives to doing these pediatric studies? Because there are some. The main one is exclusivity, which

was actually finalized under the Food and Drug Administration Modernization Act of 1997. The agency will also and has waived user fees for supplemental applications that come in for pediatric use.

What are the penalties for sponsors who do not comply with the 1998 regulations? Well, there can be an injunctive action. The product can be considered to be misbranded, and one could go to court and the federal courts can require these sponsors to do the studies and submit data or they will suffer contempt and fines and other types of adverse outcomes.

The agency will specifically, though, not withdraw approval. It's not like the accelerated approval that's conditional upon doing the required phase IV studies to confirm the surrogate. In this case, it would not be feasible or possible to withdraw an approval if it has already been shown to be safe and effective in adults. So, there isn't really that particular stick that is available in the accelerated approval regulations.

Now, exclusivity has been a very important tool towards getting pediatric studies. Exclusivity, like I said, was finalized when FDAMA was signed into law in November of 1997, and it is a very large incentive for manufacturers. It calls for tacking on an additional six months of exclusivity whether it's orphan drug exclusivity

or six months of additional marketing protection under the patent protection for any drug that qualifies.

There are specific procedures that have to be followed for a particular product to qualify for exclusivity, and there's a guidance document that the agency issued called Qualifying for Pediatric Exclusivity under 505A of the FD&C Act. I'm putting this there because in the next slide you'll see why -- well, actually before you do that, let me just make this point.

If the companies perform the required studies to be eligible for exclusivity and those studies are done and they're inconclusive or they actually fail to show that there is benefit in pediatric patients, they will still get the exclusivity. They don't have to have a positive outcome in those studies. They just have to do those studies according to the specifications set forth by the agency and they will get this additional six months of exclusivity.

Now, there are some important differences between the rule and between the exclusivity provisions of FDAMA. The rule is mandatory. The exclusivity is voluntary. Any company can request it. They can ask for it. The agency can have discussions with those companies who are thinking about doing studies to get exclusivity, but they don't have to do it. As a matter of fact, they

can think it out and say, we thought about it and we're just not going to do the studies, and that's their prerogative. But it's not the case under the rule.

Under the rule, the studies that have to be done are only for the drug and indication being sought. One is not going to require things that are not in that particular marketing application, other indications where there may be utility but are not being pursued by the company.

Under FDAMA, it's the active moiety that is under question. Again, this is not so much an issue for biological products but for drugs when there are sustained release and suspensions and inhalations and suppositories, all types of things. They all have the active moiety. When the sponsor does studies, as part of the exclusivity, the required studies, they will get exclusivity for all the active moieties, all formulations of this particular product. So, even if some of the formulations are not used in pediatrics because they've done their necessary studies on those formulations that are felt to be useful in pediatrics, they get exclusivity on the whole shebang. And so, that's why there's a very large incentive.

Now, the other important difference is here. The rule applies to all drugs and biologics. Under FDAMA, it only applies to products that are under 505 of the FD&C

Act. Biologicals are under the authority of the Public Health Service Act. The bottom line is that almost all biologics are not eligible for exclusivity. For our products, we don't have this great incentive that's actually been extremely successful with my colleagues in the Center for Drugs for getting the studies. When I say extremely successful, in all the years from 1994 on, there have been very small numbers of applications that contain appropriate studies in pediatrics. But since FDAMA went into effect, there has been well over 100 applications -- excuse me -- not marketing applications, but well over 100 requests from the agency -- it's very complicated and I'm screwing it up royally.

There has been a lot of interest in doing the pediatric studies to get the exclusivity and there's a lot of development and a lot of studies underway. FDAMA was only signed into law in 1997. A few of those have now gone on to have the pediatric data to be submitted and have gotten their exclusivity, but there are many, many others that are under development. The studies are underway.

And there's a real incentive because for some of these products, exclusivity is about to expire, and if it expires you don't get it added back on again. If it expires, you've kind of lost the ball game. So, it's very important to get these studies in and the data submitted to