FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PREGNANCY LABELING SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

9:15 a.m.

Tuesday, March 28, 2000

Crystals Ballroom
Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

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ALSO PRESENT:

MARY TETER, D.O.
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C O N T E N T S

P R O C E E D I N G S

(9:15 a.m.)

DR. GREENE: Good morning. I'd like to thank everyone for coming and call the meeting to order. My name is Mike Greene and I'll be the chair for your meeting.

I think the first order of business is -- is Jane going to do the conflict of interest statement, or are you going to do that? Okay, fine.

DR. TITUS: I'm Sandy Titus and I'm with the Advisory Committee staff.

Regarding this meeting, the following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Since the subcommittee's discussion will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to all pharmaceutical firms and their products, in accordance with 18 U.S.C. section 208, general matters waivers have been granted to all special government employees participating in the meeting. The general matters waivers permit them to participate fully in today's discussions.

A copy of these waiver statements may be obtained by submitting a written request to the agency's

Freedom of Information Office, which is located in 12A-30 of the Parklawn Building.

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

DR. GREENE: Thank you.

The first speaker this morning will be -- fine. Before we get started then -- I was not sure whether you wanted everybody to introduce themselves. Why don't we do that then? Why don't we start all the way at that corner, please.

DR. HOUN: Florence Houn, Director, Office of Drug Evaluation III.

DR. KWEDER: Sandra Kweder, Deputy Director, Office of Drug Evaluation IV.

DR. KENNEDY: Dee Kennedy. I'm with the Pregnancy Labeling Team.

DR. HAMILTON: Holli Hamilton, Pregnancy Labeling Team.

DR. DeGEORGE: Joseph DeGeorge, Associate Director for Pharmacology and Toxicology in the Office of Review Management.

DR. RODRIGUEZ: Evelyn Rodriguez, Director of the Division of Drug Risk Evaluation II in OPDRA, Office of Post-marketing Drug Risk Assessment, at CDER.

MS. CHAMBERS: Christina Chambers representing the Organization of Teratology Information Services.

DR. LEMONS: Jim Lemons. I'm a neonatologist and Director of Newborn Intensive Care Programs in Indiana University and chair the Committee on Fetus and Newborn for the American Academy.

DR. ANDREWS: Elizabeth Andrews, Director of Epidemiology at Glaxo Wellcome, also the President of the International Society for Pharmacoepidemiology.

DR. WEISS: Sheila Weiss. I'm an assistant professor and epidemiologist at the University of Maryland.

DR. SPONG: Cathy Spong. I'm a perinatologist, as well as a program director for the Maternal Fetal Medicine Unit Network at the National Institute of Child Health and Human Development, National Institutes of Health.

DR. FRIEDMAN: Jan Friedman. I'm Professor of Medical Genetics at the University of British Columbia and Director of the TERIS project.

DR. TITUS: I'm Sandy Titus. I'm with the FDA, the Advisors and Consultants Staff.

DR. GREENE: And I'm Mike Greene. I'm a

maternal fetal medicine subspecialist at Massachusetts General Hospital in Boston.

DR. MILLS: I'm Jim Mills. I'm an epidemiologist at the National Institute of Child Health and Human Development.

MS. CONOVER: Beth Conover. I'm a genetic counselor and I run the Nebraska Teratogen Information Service.

DR. MATTISON: Don Mattison. I'm the Medical Director of the March of Dimes.

DR. MONTELLA: Karen Rosene Montella. I'm the Chief of Medicine at Women & Infants Hospital at the Brown University Hospital, and we teach medicine residents to take care of sick pregnant women and run a fellowship.

DR. MITCHELL: Allen Mitchell, Director of the Slone Epidemiology Unit at Boston University.

DR. WIER: I'm Patrick Wier. I'm a reproductive toxicologist for SmithKline Beecham Pharmaceuticals.

DR. WISNER: I'm Kathy Wisner. I'm Professor of Psychiatry and Reproductive Biology at Case Western Reserve University.

MS. SCOTT: I'm Julia Scott, President of the National Black Women's Health Project, and a consumer representative on this committee.

DR. ROGERS: I'm Audrey Rogers. I'm an epidemiologist at the National Institute of Child Health and Human Development, and I was a government representative to the Antiretrovirals in Pregnancy Registry.

DR. CRAGAN: I'm Jan Cragan. I'm a medical officer in the Division of Birth Defects, Child Development, Disability, and Health at CDC.

DR. HAMMOND: I'm Mary Hammond. I'm a reproductive endocrinologist in Raleigh, North Carolina.

DR. JONES: I'm Ken Jones. I'm in the Department of Pediatrics at the University of California, San Diego.

DR. SHARRAR: I'm Bob Sharrar. I'm Senior Director of Worldwide Products Safety and Epidemiology for Merck & Company, Incorporated.

DR. WADE: I'm Nancy Wade. I'm a pediatrician in the AIDS Institute, New York State Department of Health.

DR. KING: I'm Susan King. I'm a pediatrician at the Hospital for Sick Children in Toronto, Canada.

DR. GREENE: Thank you.

Now I'll introduce the first speaker of the morning who is Dr. Sandra Kweder from the FDA.

DR. KWEDER: Good morning, everyone. I'm Sandy Kweder. As I mentioned before, I'm the Deputy Director of

the Office of Drug Evaluation IV, which I know means nothing to any of you. We oversee the regulation of all products to treat infections in three divisions.

But the other job that I have is I'm the Director of the Pregnancy Labeling Team, which is a crosscutting group within our organization that is charged with dealing with matters related to collection of data and labeling drugs for use in pregnancy.

This morning I want to begin by introducing what our goals are for this meeting. First, we're going to spend a little bit of time giving you a general update on FDA activities related to pregnancy labeling, but the labeling itself won't be the major focus of the meeting.

The more important subject over the next few days is collection of data to address safety of products in pregnant women. In particular, we'll focus a lot of the discussion on pregnancy registries. We're using as a springboard for that discussion a draft guidance document that many of you have already seen and some of you who are on the Reproductive Products Advisory Committee have already had an opportunity to comment on, at least briefly. We've structured some of the questions for you to help get your feedback on the document as we move towards finalizing it.

Then beyond that, we think that this is an

appropriate forum to engage you in a discussion that's much broader about strategies for collecting data related to safety of products in pregnancy, thinking about how we can work with those running studies or thinking about studies to get the most out of each effort, and thinking beyond some of the current models that most of us think of when we think about registries or surveillance.

The goals for my talk are really within that first goal of the meeting, in the way of updates. I'm going to give you a flavor of our progress on a new model for labeling, and I'll also then move on to discuss some of our ongoing activities related to data that would feed into those models, some about registries, but beyond that.

Now first, though, I want to point out that there are a few people at the table who weren't at the table when this committee last met, and those are Holli Hamilton and Dianne, or Dee, Kennedy. We have so much activity going on at the agency related to this general topic of pregnancy and drugs in pregnancy that we've been able to secure two full-time staff to work on this with me. This is only a piece of my job, but Holli and Dee are pretty much full-time committed to this. They both started in October of last year.

Holli comes to us from our Division of Anti-infective Products. She's an infectious disease physician

and an epidemiologist who is well versed in a lot of the methodology and clinical issues surrounding use of products in pregnancy.

And Dee Kennedy is a pharmacist who many of you may have encountered at FDA before. She spent many years in our Post-marketing Division. When you think Dee Kennedy, I think MedWatch. For those of you who know what MedWatch is, Dee invented MedWatch. She invented it and then she directed our MedWatch program for a number of years, and I feel that we are really lucky. I about turned cartwheels in the office when she said that she had come to work for us. So, that's some good news that I have.

Now, to get to the proposed label concept that many of you had an opportunity to comment on last June, the next few slides are just reminders of what that was. Our goal in moving away from a model that uses letter categories to describe risks or appropriate use of products in pregnancy is to develop a format that has structure and organization that we can adapt to widely varying bodies of data that might be available for a product and for products that cross vastly different disease states.

Specifically, our goals are, in the labeling, to distinguish clinical considerations from risk information, attempt to provide different levels of information for different needs that users may have, and

finally to use narrative text to describe and provide information as opposed to simplified letter categories that we don't think facilitates sound risk management.

The model that we showed you has three basic components that would be incorporated into each label. One, it would be clinical considerations, a brief section that would link risk assessments to practical application that might be useful for a prescribing or advising clinician. A summary risk assessment that would incorporate both human and animal data into the risk assessment and clearly state what the relevant factors were in arriving at that assessment. And then the third section would be a brief summary or discussion of data to convey the underlying data that went into the risk assessment.

I have a few bullets here that I think summarize most of the discussion that this committee had about that label format and content. In general, I think there was agreement that we were off to a good start. You advised us to give clinical directives and advice sparingly. As we've tried to move along, I will tell you I'm the hand-waver. Remember what they said. We have to give this advice sparingly. My colleagues are sick of me. But I think that was one of the major messages we took from that meeting last year.

I think that through much of the discussion,

you recognized the importance and challenge of us developing an approach that would lead to consistency across labels, and toward that end, there might be a role for some sort of standardized terminology, perhaps in the risk assessment statements, but that we would need to do some more work on that.

Since June, we have been working on this extensively. I will tell you this is extremely difficult. We have a group of about eight people that meets every other week to hash through different iterations of models and where are we going, how do we get there. But what I have on this slide is what I think have been the key decision points that we've had to confront as we've tried to move from a concept paper to what I would call a truly robust model that would be applicable.

First we had to make a distinction between what elements would actually require a regulation because this all does require that we develop a new regulation. That isn't easy. And we want to be careful that we don't box ourselves in to a point where we have to do that again in a couple of years. So, we need to tease out what are the components of this that actually require a regulation, and what are those that are more appropriate for what we call a guidance document, something that's more flexible, the "shoulds" not the "musts," the things where we need to be

able to have some give and take.

We need to sort out, as we move forward, how would we exactly implement this. It would be an impossible task to say that starting tomorrow, all labels need to have this new format. Companies couldn't handle it. We couldn't handle it. We couldn't review them all and do the project justice. So, figuring out how to do that is a challenge.

In all of this, we need to figure out, as we think about what needs to be in that label, how to make room for human data and experience because most labels don't contain human data and experience. The human data and experience that usually clinicians are interested in or that is available to address considerations in pregnancy is not the same kind of data that you see in the rest of product labels. They aren't controlled clinical trials and that makes a lot of people uncomfortable. People like certainty.

Then, of course, how specific to be in clinical considerations remains something that we grapple with every time we meet.

Now, I know that all sounds really pointy-headed and bureaucratic, and you guys are probably thinking, yes, but come on, let's just get on with it. So, why is this so hard? Just make a decision. But I think

that there are some reasons why this is so difficult.

One is the complexity of the science and the context of use of this information really mandates that we be very clear as we give guidance to companies and to our colleagues internally about how to write a label for use in pregnancy.

Yet, uncertainty predominates in the data that are likely to be available. Animal data, for the most part, continue to be and will continue to be the basis for most risk assessments, and the human data we have available are not common and they are scattered all over the place in the literature in a variable quality. Even when there are both animal data and human data, I think it's fair to say that experts often disagree on their interpretation which adds to the complexity of this.

Yet, we recognize that the breadth of user needs out there for people who are prescribing or considering taking medicines is great and that we need in the process to leave room for their clinical judgment about what is best for patients.

So, why does it take so long? Well, I've told you it's complex. For God's sake, it has been almost a year.

I think one of the things in this complexity that we are coming to terms with, particularly as we begin

to think about making room for human data, is some of this really involves a paradigm shift in our thinking. Really when you think about the topics that we're addressing today in the context of labeling, we are moving our labeling from and our data collection efforts from a search or a hunt for the smallest and largest detectable toxicity to coming at this from a different view. How can we get our arms around what the margins of safety are? And I think that's a very different way of looking at this, and that's one of the reasons this is so difficult. We're approaching this differently.

Also, regulations. I will tell you, as someone who has been around the FDA for a while, regulations are never easy to write. They take a long time. Even once we make decisions ourselves, you wouldn't believe how many other people who know nothing about the subject will have to look at this and comment on it, things like financial impact. There's a person who spends all their time thinking about what is the financial impact to many parties of any regulation we write. So, that sort of thing has to happen.

This is also one of several very large labeling initiatives that we have going on at FDA, and we need to make sure that they dovetail and don't contradict each other.

Increasingly, as we move forward, we are recognizing that it is not enough just to change a regulation that says what should be in a label. Efforts to enhance data collection and facilitate submission of that data to the FDA absolutely must be part of this effort. Just saying here's the way it ought to look on a piece of paper is not enough. The goal is to have more information.

So, toward that end, I've talked about our label model development and where we are going with that. I want to give you a flavor of what some of the activities are that we're engaged in to improve data and to expand thinking in this area internally and externally about what are some other aspects of risk management that are appropriate for pregnant women.

In the area of improving data, I think that historically and currently the main focus does remain on fetal and infant outcomes following exposure in pregnancy. Registries are one of the principal tools available as methods of surveillance to collect this type of data, but they do remain rare. We have historically and continue to rely on product sponsors to conduct those surveillance efforts. Where there are other types of data in the literature or where others have conducted similar studies, currently there is no specific regulation or incentive for companies to come to us with those data and ask us to

include those in labeling, and that's a problem that we're beginning to try to address.

As we begin to do that, we recognize that, in addition to this paradigm shift, we have to confront and engage in discussion with folks like yourselves about what we see as somewhat a controversial area of the value of normal outcomes when the numbers of exposures are small.

Now, in the area of improving registry data, we have a draft guidance document that you have in your packet and you'll have an opportunity to address later this morning. Dr. Rodriguez will walk you through it. That is one tool that we have toward enhancing data.

FDA also has a new regulation that's actually circling through the agency -- it hasn't been published yet, but we've already promised that we will publish it -- that will require sponsors to address all data relevant to safety of products for special populations. And pregnant women is listed as one of those special populations. That regulation will be critical to getting data into labels. It is essential.

Right now what we get is oftentimes -- companies are required to send us annual reports on their products, safety reports. All companies don't do this, but it's not unusual for someone at a company to do a literature search on a product and maybe buried in a stack

of reprints like this that comes in among four or six volumes toward an annual report, there will be a couple of articles about a drug in pregnancy or something about it. But there's nothing that says that companies must take that data and specifically make an evaluation of it and propose labeling changes on the basis of that data for use in pregnancy. And so most don't.

We also feel that we need to expand our discussion of registries. This meeting is one way to do that. We are also engaged in discussions with groups outside of the FDA like the CDC and the March of Dimes to begin to think about other models for registries and how we can collect data. We also are beginning to work with the International Society of Pharmacoepidemiology to get some other expert opinion, particularly in the areas of methodology and how to do this well.

What about thinking more broadly? Well, I've said that registries remain our principal tool and a major focus, and they are very important and can be helpful for collecting certain types of data such as general pregnancy outcomes or fetal outcomes and providing us with some general margins of safety that are rather broad brush.

But there are other elements of safety and rational prescribing that need to be considered, and two of them I have listed on this slide. One is pharmacokinetics

and pharmacodynamics of drugs in pregnancy, and the other is what about lactation. We're just beginning to engage in discussions and try to figure out how we can help enhance data in these areas.

But I think most of you who have taken care of pregnant women or been pregnant yourself know that once the patient and clinician cross a threshold and make a decision that a pharmacologic intervention is necessary, then the question becomes what dose. If you go through the literature and textbooks that talk about prescribing in pregnancy, most of them say prescribe the lowest effective dose. Well, the lowest effective dose in the general population of non-pregnant people may not be the best dose for the pregnant woman. Particularly for products that have a narrow therapeutic margin but perhaps there is therapeutic monitoring by drug levels is impossible, there is a risk for certain types of products that a woman may be taking a drug and receiving no benefit, exposing her baby to an effect unknown for very little benefit. We think that that's not the way people ought to be prescribing. We think that there ought to be better information out there for people who need to prescribe particularly for drugs that are used often or where therapeutic margins are narrow.

The medical literature in this area on dosing

in pregnancy, pharmacokinetics, pharmacodynamics, is quite limited, but where it exists, for the most part, it does not appear in product labels. My favorite example of that is amoxicillin. There is plenty of PK information out there about amoxicillin. Therapeutic levels in antibiotics are pretty well characterized and described, and yet most clinicians don't know that there's information out there about the pharmacokinetics of amoxicillin.

Entering into data collection and research in this area are, of course, the physiologic effects of pregnancy and how those may make a difference in what happens in the pregnant woman when she takes a medicine. I often think of this as, the pregnant state is like this little window of -- like the most female state and the most intense hormonal effects on metabolism of the drugs are likely to be seen in pregnancy. There is at least one study that shows that one of the isoenzymes, the P450, is changed when women are pregnant, and that may be important for some medications.

So, what is FDA doing in this area? Well, the new safety regulation will help us in this area. It will encourage companies to bring those sorts of data that are out there in the literature to our attention and begin to evaluate them.

We are also collaborating with the NICHD to try

and facilitate more research in this area. Dr. Cathy Spong later this morning will be telling you about some of their activities, including a workshop that they're going to be sponsoring this fall to try and bring together experts in obstetrics, other fields, and clinical pharmacology to try and develop a research agenda in this area.

Later in the fall, FDA, NICHD, and probably several other groups are going to sponsor a larger workshop to try and generate broader interest and sort of assess the state of the art in this area.

We are already planning a workshop or symposium at the annual meeting of the American Society of Clinical Pharmacology and Therapeutics for spring 2001.

Then on to lactation. I think it's fair to say, and I think this is a nice way of saying, that product labels are rarely informative in this area. I've had people say to me, well, you know, it may as well not even be in there. And you know what? For the most part, it's true. Those product labels say very little that's helpful about this.

Yet, increasingly the health benefits of breast feeding are recognized. Healthy people 2010, the American Academy of Pediatrics, and on and on and on increasingly encourage women to breast feed longer rather than shift to formula after the first few weeks of life. It's safe to

say that many women need prescription medicines while they're breast feeding and we know very little about how much of any given drug gets into breast milk and how the developing infant metabolizes those products once they're there, once they're ingested. Those effects may be very different in the neonate and the 6-month-old.

The way I think of this from where I sit is lactation is sort of the next frontier for us. The FDA has a large initiative ongoing in pediatrics. Fortunately for us, the pediatrics initiative is housed in the same part of the organization that we are, which makes things very convenient. We think that thinking about the safe use of products from a public health standpoint, there is a natural link from pregnancy to nursing mother to baby. So, we need to think about the science and the safety of these products as a continuum.

This is an area that we feel is really uncharted territory for us. We are beginning to work with the pediatrics team to work on this collaboratively internally and try to integrate our concerns, first, by assessing the state of the art in science in this area. We know that there's a lot out there but it doesn't come to our attention in any organized way. We will likely, as part of our efforts to begin to explore this, bring together members of this committee with our Pediatrics

Advisory Committee hopefully in the fall of this year to begin to explore where we need to go with lactation.

Then I don't think I would be complete without just making reference to dietary supplements. Many of you are aware that there is a public hearing on Thursday of this week that is to take testimony on a new proposed regulation by our Center for Food Safety and Nutritional Products related to structure-function claims for dietary supplements and how those are distinct from disease or treatment claims, which would make something a drug, but specifically the issue at hand for Thursday is how do we deal with pregnancy in the context of structure-function claims and yet still ensure that these products are used safely. That is not a topic for the meeting over the next two days. There is a very formal, organized public hearing with the Center Directors from Foods and Drugs who will take public testimony on that on Thursday.

So, in summary, I think we are making steady progress as we move toward developing a labeling model for pregnancy. We recognize and are trying to attend to an increasing emphasis on addressing data needs, specifically what we consider the broader area of risk management of drugs in pregnancy. Elements that we are involved with toward doing that are trying to find ways to encourage the development of sound registries, but also think outside of

usual models for data collection on fetal outcomes.

We also think it's important to find ways to increase pharmacokinetic, pharmacodynamic, and dosing data in pregnancy and begin to develop scientifically a regulatory framework for dealing with lactation.

One of the things that's increasingly apparent to us is that we can't do this alone. We really need to work with people like yourselves and collaborate with other groups who share similar interests to make progress in these areas.

So, again, just to introduce the rest of the meeting in the way of other updates that will be on the agenda this morning, Joseph DeGeorge will give you an update on some activities related to work in the preclinical area, reproductive toxicology, that will feed directly into our labeling attempts. Cathy Spong from the NICHD will speak about PK/PD and their efforts in that area. Dr. Evelyn Rodriguez will walk you through the guidance document on pregnancy registries to help launch the discussion of that topic. And then later in the meeting, we have a number of speakers lined up to help stimulate your thinking about a broader discussion of strategies for data collection, how to get the most out of each effort, and thinking beyond the current models for registries, particularly that we know of, sort of -- you

know, always a pharmaceutical company, one drug, one company.

So, thank you very much.

(Applause.)

DR. GREENE: Thank you.

Are there any questions for Dr. Kweder?

(No response.)

DR. GREENE: Thank you.

We move on now to Dr. DeGeorge please.

DR. DeGEORGE: Good morning.

My task today is to actually give you an update on what our nonclinical efforts are in evaluating reproductive risk, and I'm not going to go through as much detail as was presented, I think, in October -- maybe it was our June meeting -- where you actually got a preview of our concept and how we were thinking about evaluating reproductive risk. But instead, I'll focus on telling you what we have done since that time in our various efforts.

As I think it's clear to everyone in this room, at the time that products are approved, we have very little information from humans on reproductive risks. In writing labels for products into the foreseeable future, we're still going to have to rely on nonclinical information in drafting that label. The focus of this meeting, of course, is mainly clinical information and its sources, but this is

an attempt to begin to reconsider our evaluation process for reproductive risk using animal information.

Our effort begins with the defining of the issue about generally we're not going to have human information. Yet, we're going to have to make some estimate of human risk. We recognize the fact, however, that not all animal risks or all animal findings represent a true human risk for reproductive toxicity, just as not all negative findings in animal studies indicate no risk for humans in the same area. And there are plenty pharmaceutical examples which demonstrate those principles.

What we also recognize, though, as a regulatory agency is we really have to have a standardized approach for evaluating risk that we can then use to communicate the relevancy of findings to humans, and that this needs to be science based within our current context of reproductive evaluation.

Now, this is just a view of the landscape of the various activities that are going on within the center. The Pregnancy Labeling Task Force, which is chaired by Sandy Kweder and Bern Schwetz, is really something that is actually organized out of the Commissioner's Office, and it has representation from all of the centers, not just the Center for Drugs, not just the Center for Biologic Products, but from CFSAN and the Commissioner's Office, and

many other people contribute to this effort.

There are a number of working groups that are tasked under this overriding committee to, in fact, generate the various documents that you have heard about in the past and will hear about today as well. I'm going to talk about the documents that are in the lighter green color, and that is the preclinical guide for reproductive study evaluation and the integrative analysis for reproductive risks. These are actually coordinated through CDER's Pharmacology and Toxicology Coordinating Committee. One is a product of our Reproductive Toxicology Committee, whereas the other is a product of an integrated group of reproductive toxicologists and generalists in toxicology information assessment.

And there are the other task forces, that which is drafting the proposed rule and guidance for labeling, the various task forces that are working on establishing registries, which you'll focus on today, and also a guidance which I think you've seen already in a draft form on how to evaluate reproductive risks from human data.

I'm going to begin with the integration working group because this document is actually fairly advanced and we plan to have our last meeting of our drafting committee this week. Then we will begin the laborious process of clearing FDA to be publicly available for draft and

comment.

The people on this committee have meet I think, since about two and a half years now, every other week for three hours late in the afternoon to try to reach a consensus on what is a reasonable approach. We've been modifying this document over and over as we get more information about new approaches and new things we need to consider.

The task for the group was really to develop something for reviewers within primarily the Center for Drugs and the Center for Biologic Products, which is where we do product labeling in terms of reproductive risks primarily, to use to interpret findings from reproductive toxicology studies in light of other kinds of information, and to be sure that in applying such an assistance or a reference document, that they would come to reasonably consistent conclusions based on an identical data set. However, I need to point out that this document, that we will hope to make available this summer, is not a guide on how to evaluate reproductive toxicology findings. That's the other document I'll talk about later on.

So, the objectives of this working group were to standardize a method for judging and evaluating the relevancy of nonclinical findings for human reproductive risk, to try to characterize those findings in the context

of the total data set that we have, whatever human information we do have, such as drug metabolism, exposure, how that relates to the animal studies and how they were conducted, and then to organize these findings in a consistent manner so that we could effectively communicate and discuss our conclusions with others, with the rest of our stakeholders.

The approach is, in fact, to enumerate and to codify thought processes which people who have seen the draft concept paper say are not that much different than what they have thought about generally in the past, but it's not been organized. We tried to group information that address similar questions. Such as, exposure information can come from kinetics. It can come from comparative biomarkers. It can come from a variety of sources. We try to group that information that addresses a particular kind of question together and separate that, in essence, from were there findings in a particular toxicology study.

It then tries to assign weights to these various groups -- and I'll go through the categories in a moment -- and then come to some consistent evaluation about what those developmental risks are for each endpoint that is normally evaluated in reproductive toxicology.

The document actually describes the overall

process. There are three flow charts that have been generated out of this document. One is are there sufficient information to even make an evaluation of reproductive risk. Not every study provides sufficient information to do that. To try to determine, where we have complete studies and there are, in fact, no findings, whether or not those studies are adequate also to say there is no apparent risk to humans. Then finally, when we have positive findings in either reproductive toxicology studies or general toxicology studies that address reproductive risk, trying to make a decision as to whether those findings do, in fact, generate some concern or risk for the effect.

Now, I'm just going to talk about the context of the proposal that is going out on the integration. This has been shared as a concept paper, and it really divides information into six groupings. We have something called signal strength 1 and signal strength 2, and that is to make sure that we give adequate weight to reproductive findings in and of themselves.

In the signal strength 1, we're looking at issues of concordance of findings across species, the multiplicity of those findings within a species, and the time dependency. Do you only have to treat once to get the effect? Or does it take multiple treatments to get the

effect? Or can the effect occur with single treatments across multiple time intervals? All those are important considerations in evaluating the risk.

We have signal strength 2. Are the findings independent of something like maternal toxicity or are they caused by it or so closely associated with it?

The pharmacodynamics of the product itself. How relevant is that to the finding? Is it an expected finding of the intended pharmacologic activity or not?

The concordance of the animal model with humans. Are they making very different metabolic profiles than the human would use with this, and can the finding be related to those differences or not?

And then finally, exposure comparisons, and of course, class alerts. Is this something that's in a class of compounds where we know there is human risk?

Now, we've presented this concept paper at a number of different forums. We first presented it in 1998 in a very general format to see whether we had thought about the right issues. We then had a presentation last June at this advisory committee. We followed that up with a presentation that was a whole day industry public meeting with FDA where we presented the approach, the details of that approach, went through case studies, and got feedback on the concept. We've since also presented that later on

that month at the Drug Information Association, and then we've had a recent presentation where more data was brought forward by industry representatives. Dr. Wier on this committee presented some of their experience with using this approach and what their issues were. And we've also made presentations to a number of scientific societies. So, we've gotten lots of feedback already on this early concept.

I would have to say that some of the feedback we received officially has been very encouraging. A number of pharmaceutical representatives have indicated that they find it useful in organizing and evaluating data. The European regulatory community has also commented on the concept paper. Individual regulators in Europe have as well. They've been fairly favorable. Of course, everyone has comments and recommendations for change. It's not unexpected.

The two major kinds of comments that we've had, though, really focus on something that was not in the concept paper and that is the use of biomarkers as exposure indicators, and we are considering that, and also views on how the factors, those six factors, are weighted, whether our approach of weighting, which counts each of those factors equivalently, is adequate or not. We'll have to address that and we are trying to address that in our

current drafts. We'll make that available when the document is available soon.

We expect, as I said, to finalize the draft within this week, at least by our group, then try to get it cleared, and hopefully have it available by July. That is probably a little bit wishful thinking, but we'll do what we can to get it out because we know it is important to have comment on it.

Once we make this draft document available, we intend to have a workshop on it to describe its application. It's a very densely written guidance, a guidance to reviewers. It needs a lot of discussion. Once we have that discussion of how it may be used, hopefully we'll get feedback that will be based on what at least our intended approach of its use is so that can advise our revisions before we go to a final document.

The other group I mentioned is our Reproductive Toxicology Committee, which is made up entirely of people who have expertise in reproductive toxicology, not generalists included such as myself. This group is working on a document as to how to advise reviewers to evaluate those studies which are reasonably done usually conducted in pharmaceuticals to specifically evaluate reproductive effects, what we used to call segments 1, 2, and 3, and now call under our International Conference on Harmonization

sections A through, I think, it's F in terms of segments, studies.

This committee serves as a resource to reviewers when they have findings. Are they relevant or not? And it is also generating the guidance so that people who are more generalists can evaluate reproductive toxicology studies hopefully by having some sort of reference material. So, the objective of this committee is to provide some reference for the average reviewer within FDA who reviews toxicology findings to have a baseline to make sure they've addressed all the important elements in evaluating those reproductive toxicology studies. The approach taken is really a systems approach for reproductive toxicity.

The various chapters are in their final stages of preparation of the first phase of preparation. They have not been seen by anyone outside that committee except as a text editor. What we still need to do is get internal review, and then we intend to seek peer review in the scientific community on this document because clearly this is a document where we need some expertise that goes beyond the agency. I would say we have a target for the first quarter of '01 to actually get some available as a general comment.

So, in summary, we have two projects ongoing.

One is integration, which is the one which will feed most directly into the efforts of this committee and the Labeling Task Force, and the other effort is our document to help reviewers understand and make sure they address all the important points in evaluating reproductive toxicology studies.

Thank you.

DR. GREENE: Thank you.

Any questions for Dr. DeGeorge? Yes, Don.

DR. MATTISON: Your slide bullet about biomarkers talked about biomarkers as integrative approaches. But as you spoke about it, you talked about the use of biomarkers for dose characterization. Those are a little bit different, and I wonder if you could maybe comment a little bit more about that.

DR. DeGEORGE: Well, I don't know that I'm free to comment to any great detail about specifically how we are incorporating biomarkers, but we think biomarkers as a general concept can be used both as evidence of exposure and relative exposure, but also as evidence of where are you on a dose-response curve in relation to an individual effect. So, biomarkers are considered within our approach in multiple elements I think is the best I can say. Does that answer your question?

DR. MATTISON: Does that also include

mechanism?

DR. DeGEORGE: No. Mechanism is a separate issue within the pharmacodynamics. The mechanism of the finding is considered one of those separate elements. It may contribute to that mechanism. Evaluation as a -- if you saw the effect which was presumably the effect related to the reproductive toxicity and you can measure some -- let's say, cholinesterase inhibition somehow is related to your effect and you could measure that inhibition, you would know where you were exactly on that dose-response curve in humans.

DR. GREENE: Other questions for Dr. DeGeorge?

(No response.)

DR. GREENE: Thank you.

We'll move on to Dr. Cathy Spong, please.

DR. SPONG: Good morning. I'd like to thank you for inviting me to give the NICHD perspective on the needs for the study of therapeutic drug use in pregnancy.

As Sandy Kweder so elegantly pointed out this morning, there are many issues surrounding the use of drugs in pregnancy. First and foremost, the use of therapeutic drugs in pregnancy is not only common, it's also necessary. As a maternal-fetal medicine specialist, I take care of patients who have high risk medical conditions, and it's very, very common to give these patients medications.

Sometimes we give these medications to treat the mom, sometimes we give them to treat the fetus. It's an area that we don't have a lot of guidance on.

Other issues include that during pregnancy there are many physiologic changes that affect drug levels. In addition, the fact that when you give a drug to a mother, there is a transfer to the fetus, and the difficulty of actually assessing that and the fetal drug levels that subsequently occur.

Finally, the issue of ethical considerations and study designs which are inherently difficult in the model of pregnancy. These are the issues that I'd like to touch upon this morning and then go into a little bit about the workshop that we plan in collaboration with the FDA.

Again, therapeutic drug use is very, very common in pregnancy and it's required for both maternal conditions, pregnancy related conditions, and fetal conditions. Maternal conditions that require therapy during pregnancy are many and varied, but these are probably the more common. Conditions such as asthma and hypertension, psychiatric disorders, and diabetes can occur before pregnancy and we're just continuing medications that patients were on prior. However, not only do you need to give the same medication, perhaps you need to change it because the medication that they were on is not considered

to be safe or efficacious. In addition, the dosage required may change as the pregnancy progresses.

In pregnancy in addition, there are other conditions that occur just because the woman is pregnant such as gestational diabetes or gestational hypertension. These can be longstanding conditions where the pregnant woman is going to be needed to be treated for a long time during pregnancy.

Alternatively, there other conditions that can be very acute requiring medications for a couple of days or a couple of weeks, not the entire time of pregnancy. Those include preterm labor and preeclampsia where the treatment is typically later in gestation, in the third trimester after the fetus is predominantly formed, or very early on such as in the condition of hyperemesis and morning sickness.

Finally, there are fetal conditions that commonly require drug therapy. These again are in two varieties: cardiac conditions where we actually treat the mom in order to get to the fetus, such as supraventricular tachycardia and complete heart block. Sometimes these fetuses need to be treated in utero and one method of treatment is actually giving the mom the medication and allowing it to be transferred to the fetus.

Also, we will give mother medication such as

impending preterm delivery where we'll give mom steroids in order to attempt to prevent respiratory distress syndrome in the fetus. This is a more acute condition where you'd give the dose once or twice as opposed to a cardiac condition where you may be giving this to the mom for the fetus for a prolonged period of time.

So, drug therapy in pregnancy is a balancing act where we're giving maternal treatment and we're weighing that upon the fetal effects. It's often better to go ahead and treat the mom if it's a maternal condition because if the mother is untreated, it may have significant impact on the pregnancy. However, the treatment that we're using -- there is little scientific for us to base it on.

I'd like to touch a little bit on the maternal physiologic changes that affect therapeutic drug administration. These include the cardiovascular system, the GI system, renal effects, as well as effects on enzymes, as Sandy pointed out this morning.

Cardiovascular changes are gestational age dependent. You get a plasma volume expansion and with that you get a subsequent decrease in serum albumin concentrations which may significantly affect certain drugs that are administered. In addition, you get an increase in cardiac output, as well as alterations in the regional blood flow. All of these have significant effects on the

pharmacokinetics of drugs.

Cardiovascular effects include plasma volume expansion. This occurs very early on, just around 6 to 8 weeks of pregnancy, and it peaks around 32 weeks of pregnancy. Again, a longstanding effect that we often wouldn't consider as occurring in the first trimester, but in fact it does. By the end time point, the increase in plasma volume is about 1 and a half liters.

In addition, cardiac output increases by 30 to 50 percent. Initially this is due to an increase in stroke volume and later on felt to be more due to an increase in maternal heart rate.

Alterations in regional blood flow include an increased in-flow to the uterus, to the kidneys, to the skin, and to the mammary glands, and a decrease in blood flow to the skeletal muscles.

Finally, looking at other systems, they include gastrointestinal changes where there is a delay in gastric emptying and an increase in transit time. So, drugs that are administered orally to patients have significant changes in how they are metabolized and how they get through the GI system.

Renal changes include an increase in the glomerular filtration rate which has a significant impact on drugs that are metabolized through the kidney.

Finally, there are enzyme activity changes that are felt to be related to pregnancy hormonal changes.

So, the consequence of all of these physiologic changes are the following. With the volume expansion, we will often get an increase in the free fraction of drug that we administer to patients. This is due to a decrease in the overall serum albumin levels.

In addition, there are clearance changes both due to the effects on the kidneys as well as enzymatic changes.

Finally, the changes in the GI system result in problems for administration of oral drugs.

The result of all of this is that often dosages need to be changed during pregnancy and throughout pregnancy.

In addition, as Sandy pointed out this morning, this doesn't stop once pregnancy ends. Postpartum you get a significant diuresis of the plasma volume that the patient had been accumulating, and there are significant impacts when patients continue to breast feed that drugs that you administer to them will also cross over to the fetus.

Finally, there's a significant variability between individuals that cannot totally be accounted for.

Next, taking the shift of administering drugs,

we need to remember the effects of gestational age. Very early on, the embryo is not totally formed. The embryo is undergoing embryogenesis and organogenesis, and toxicities are very different than when drugs are administered later, although the fetus does continue to develop both in the second and third trimester as well as a neonate.

The maternal-fetal transfer of drugs is well known. There's placental transfer as well as once it gets into the amniotic sac, transfer across mucosal membranes, such as the GI tract, and early on in pregnancy, before 25 weeks, there's actually transfer across the fetal skin. Finally, after pregnancy is over, there is transfer via breast milk when lactation is occurring.

Monitoring fetal drug levels obviously is very difficult since the pregnancy is self-contained. We often rely on the clinical exam and on the response, just evaluating and monitoring the fetus externally using sonography. Again, we aim for the lowest effective dose because our feeling is that giving less is better, but this may not be the case if it's not being effectively treated.

We can evaluate the fetus using ultrasound. We can also do cordocentesis where you're sampling the blood of the fetus, but this has risks whenever you're doing anything invasive.

Ethical considerations and study design are

very important when you're looking in pregnancy. Again, drug labeling is inadequate for our guidance in pregnancy, and the research that's available on the drugs in pregnancy is sparse. Pharmacokinetic studies in pregnancy, as we've mentioned many times this morning, are inadequate, and this is in part due to incredible difficulties getting IRB approval for these studies.

Finally, pharmaceutical companies are not particularly interested in doing these studies, as it's much easier to say just don't use these drugs during pregnancy rather than taking on the liabilities of giving a statement as to whether or not these drugs are safe in pregnancy.

From all of this, the FDA and NICHD have found that research on pharmacokinetics and pharmacodynamics of therapeutic drugs is very important. We focused on the second and the third trimesters of pregnancy because inherently looking at the first trimester of pregnancy when organogenesis is ongoing brings problems in and of itself. So, initially we'd like to focus just on the second and the third trimester.

Again, we are focusing on a workshop to be held in the fall of this year where we'd like to discuss ideas and generate research interest and activities looking at drug use in pregnancy. Ultimately, we'd like to generate

certain mechanisms for the study of pharmacokinetics of drugs in pregnancy. This will be followed up by an FDA meeting hopefully in November.

So, the bottom line is that therapeutic drugs are common and required in pregnancy. Research is needed to evaluate the efficacy, the safety, and the required alterations in dosage, timing during pregnancy. These are issues that pharmaceutical companies will never provide.

Thank you.

(Applause.)

DR. GREENE: Any questions for Dr. Spong, please? Yes, Don?

DR. MATTISON: You began by laying out maternal pregnancy related and fetal conditions for therapy, but then ended by talking about the fact that the workshop and the initiative between the NICHD and FDA focuses on the second and third trimesters. Yet, maternal conditions, fetal conditions, and pregnancy related conditions can be expressed in the first trimester. I guess it would seem to me that one of the complications of understanding how to improve treatment would have to focus on where the systems were changing the most rapidly in terms of their impact on both kinetics and dynamics. Comments on that?

DR. SPONG: I certainly agree that research in the first trimester is equally as important as in the

second and third. My two comments are, one, the most pregnancy related changes occur in the second trimester -- that is, on the mother, on the cardiovascular system, the GI system, the hormonal changes. They're mainly more in the second and third trimester.

In addition, to get research done in the first trimester, to get studies done is going to be incredibly difficult for IRBs to approve these studies, and we agree that that needs to be done. But we've got to start somewhere, and let's start somewhere that's not as touchy. So, we're going to focus on the second and third trimester. We'll go back to the first trimester, but the second and third trimester is equally as deserving of study and less difficult for the IRBs.

DR. MATTISON: And then just a definitional question. One of the slides that has the check mark and says, "result: dosing changes," do you mean both frequency and amount?

DR. SPONG: Yes.

DR. MONTELLA: I actually would like to comment further on the point about the first trimester because I do think it's a really valid point. You are changing certainly metabolism of drugs and volume is on its way up. So, you really are changing during that time. It's also the time at which people are inadvertently exposed to drugs

most frequently. It's also the time during which there's a lot of bias against use of needed drugs in terms of trying to lessen exposure, and it's a time when you may be specifically underdosing people or withholding drugs. So, I think it's a really critical period for us to look at.

DR. SPONG: We certainly agree. We absolutely agree. Our reason for choosing the second and third trimester is just to start the interest. If you cannot get anything going, you're never going to get to the first trimester. We realized that no matter what -- this has been a very neglected topic for a long period of time. If we can at least get something going where it's not so difficult in the second and third, the first will follow. We absolutely agree.

DR. MONTELLA: I certainly applaud that effort.

DR. SPONG: We absolutely agree.

DR. FRIEDMAN: Just to follow up along the same line, I'm not sure I understand the statement that you made several times about the difficulties with IRBs. It seems to me that if you have a group of women that are being treated because they need to treated or they have already been treated anyway, gathering information on drug metabolism, on elimination, and so forth from the mother shouldn't present tremendous ethical problems.

DR. SPONG: Gathering information on currently

treated drugs is probably not going to be difficult, especially noninvasively. But when you start to talk about labeling drugs, talk about trying different drugs, yes, there is going to be -- obstetricians typically use things that work. And we've just used the same drugs typically for a long period of time because they've worked. The exposure of a woman to a drug because you wanted to test that drug is somewhat difficult.

DR. FRIEDMAN: Well, even the things that work don't always work.

DR. SPONG: That's true.

DR. FRIEDMAN: And the things that work we don't often have a lot of information on. It just hasn't been collected even though the drugs have been used for a long time.

DR. SPONG: This is very true.

DR. FRIEDMAN: And it seems to me that there aren't tremendous IRB restrictions for gathering that information. That ought to be an area of intensive research.

DR. SPONG: I agree. Gathering information, as you describe, would not be difficult for an IRB and certainly should go forward.

DR. GREENE: Other questions for Dr. Spong?

(No response.)

DR. GREENE: Thank you.

We now have some time for open public hearing comments. We've been notified of one person who would like to speak, Dr. Mary Teter. At this time I'd like to give her an opportunity to speak, and also to ask if there is anyone else who would like to speak, to please let us know at the front desk.

I think many of you will have copies of her handouts in your packages. I think there was a shortage. I'm not sure everybody has them, but I think most people do.

DR. TETER: We do have a few extra copies if you need them.

Thank you very much for allowing us to speak today. My name is Mary Teter. I'm a physician and a Director of Drug Safety and Pharmacovigilance with Bristol-Myers Squibb Pharmaceutical Company in Princeton, New Jersey. By medical training I'm a pediatrician, but I'm here today to present comments from PhRMA, the Pharmaceutical Research and Manufacturers of America, and we would like to comment on the FDA draft guidance for industry on establishing pregnancy registries.

A little bit of background about PhRMA. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Members invest

over $26 billion annually in the discovery and development of new medicines. Because of our commitment to patient safety with the products we develop and market, we are interested in the use of pregnancy registries as a research methodology in specific circumstances.

First, a few general comments on pregnancy registries. PhRMA supports FDA efforts to provide consistent guidance to industry regarding pregnancy registries. We recognize the potential of a guidance document to enhance the validity and utility of data obtained through registries, and we hope that a revised guidance document will minimize confusion about the regulatory status of adverse events reports received through pregnancy data collection.

We would like to touch on a few points, the first of which is the definition of a pregnancy registry. A clear and concise standard definition of a pregnancy registry should be developed with an explanation of how a registry differs from standard clinical trials and other epidemiologic methods, such as cohort studies. Key features of a pregnancy registry as outlined in the guidance indicate that it must be prospective in nature and include active collection of data. However, pregnancy registries are alternatively described in the guidance as: A, a system to collect information on specific

drug/biologic exposures; and B, cohort studies of women exposed to a particular drug compared with a nonexposed cohort.

Similarly, the difference in design between an active surveillance program for signal detection and hypothesis generation and study for hypothesis testing is blurred in the guidance document.

A pregnancy registry should be an efficient means to assess, with sufficient statistical sensitivity and specificity, the relationship between exposure and pregnancy.

It should be made clear that registries do not have to have concurrent internal comparison groups. That comparison can be made using external rates. And noncomparative registries can be used for hypothesis testing.

Comparative cohort study design may be more appropriate when there is sufficient suspicion of a signal that requires confirmation.

The second point that we would like to address is the objectives of pregnancy registries. A statement of the scientific and regulatory objectives of pregnancy registries, including clear guidance on when a pregnancy registry is needed and the information to be generated, should be presented in the guidance. The limitations of a

pregnancy registry should be clearly described.

The public health need for a specific registry or study should be defined by the likelihood of drug use during pregnancy and the potential risk to the mother or fetus. Potential risk should be based on a drug's chemical structure or principal metabolites, pharmacologic class or similarity of its mechanism of action to other drugs in a chemical class, animal toxicity findings, or human case reports of abnormal outcomes.

Registries should be established for new products when there is a signal detected or suspected. Registries should not be required for all products. In general, we see no need to implement registries for well-established marketed products where no risk has been identified.

The specific goal of a registry will drive design, data collection methods, and the enrolled population. All registries need not be alike and there should not be one standard design. However, clear endpoints for study conclusion must be established prior to registry initiation.

A registry guidance should also describe how information on normal pregnancy outcomes will be disseminated to medical providers or used to support product-specific labeling.

Recognizing the limited experience with pregnancy registries to date PhRMA urges FDA to assess, in conjunction with industry, the value and experiences gained with pregnancy registries using specific metrics.

Finally, we'd like to address an area that's very important to us and that is adverse event reporting. It's very important for FDA to provide a clear discussion of the regulatory requirements for adverse event reports arising from pregnancy registries and the rationale for these requirements.

FDA has not addressed by regulation the reporting of adverse events from pregnancy registries, and FDA's guidance to various sponsors may not have always been consistent in the past.

The guidance document does not clarify whether pregnancy registries should be considered post-marketing studies or part of an active surveillance program.

We do have recommendations. PhRMA strongly recommends that FDA consider reports from pregnancy registries to be solicited reports as outlined in FDA's Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Clarification of What to Report, which was issued in August 1997.

Under this guidance, solicited reports are to

be handled in the same way as reports from clinical studies and only submitted to FDA on an expedited basis, that is, within 15 days of learning of the event, if they involve serious, unexpected events for which the sponsor or the investigator concludes that there is a reasonable possibility that the drug caused the event. However, all adverse event data should be filed as part of a complete summary of the registry experience, at the conclusion of that registry.

In summary, we ask FDA to consider and review our comments on the guidance document, with particular attention to three areas: one, the definition of pregnancy registries; two, the objectives of a pregnancy registry; and three, how to handle adverse event reports arising from pregnancy registries.

Additional commentary has been submitted by PhRMA to FDA in a letter to the docket which was dated August 31, 1999, but we certainly appreciate the chance to participate in this meeting and to present our comments directly to the committee. Thank you.

(Applause.)

DR. GREENE: Thank you.

Any questions for Dr. Teter, please? Jan?

DR. FRIEDMAN: I have concern about your recommendation or your statement that there's no need to

implement registries for well-established marketed products where no risk has been identified. How do you decide if no risk has been identified for most products when there haven't been any studies?

DR. TETER: Well, I think obviously that's an area that's open for discussion. But certainly we would be driven by or think or approach the need for a pregnancy registry where there is some suspicion that there may be a risk. Many products have been marketed for many years and have been used in pregnant women, and there are not reports of adverse effects reported. So, I don't think that that would be a place to start with a pregnancy registry. We would feel that the place that that should be directed would be where there is a suspicion of a risk either based on animal data or previous human exposures.

DR. WIER: I just follow up on Jan's comment, and that is, historically I think we're hard-pressed to find many examples, perhaps aside from isotretinoin, where risk was expected, anticipated, identified in advance. Virtually all known human teratogens were not expected to be that. And I would just urge that caution and thinking.

DR. GREENE: Other questions or comments?

(No response.)

DR. GREENE: Thank you very much.

DR. TETER: Thank you.

DR. GREENE: We are right on time, quite remarkably. I want to thank all of the morning speakers for remaining right on time.

We have a minute or two if there is any other further public comment, and then we'll take our break as scheduled on our agenda. If there's no other public comment, thank you. We stand adjourned for 15 minutes.

(Recess.)

DR. GREENE: Could we reconvene, please? Let's get started please with the second half of the morning.

The next speaker will be Dr. Elizabeth Andrews. Dr. Andrews, please.

DR. ANDREWS: Thank you. One thing I'm going to do is point out that there are a couple of themes that came up in the earlier session that you'll see as common threads in this talk, and one is Dr. Kweder's comment about understanding the general margins of safety. The other was from Dr. Spong, you've got to start somewhere. What I'd like to do is talk about our experiences with our registries.

My first lesson I think is that had we thought about the implications of the use of the term "registry" when we created our first registry, we probably would have called it a follow-up study rather than a registry because registry, as a term, leads to a lot of confusion.

What I'd like to do is to illustrate one approach to pregnancy follow-up studies using the examples from our own experience, and then I'd like to describe a few of the practical lessons that we've learned from hands-on experience over the years. Then I'd like to spend a couple of minutes talking about future possibilities on the horizon, and then to identify three key issues that I think simply must be addressed if we are to move ahead in the direction that the FDA, the CDC, the pharmaceutical companies, and providers and women would like us to move in, and that is, providing much more information that's available in decision making as regarding medicines in pregnancy.

First, let me mention that pharmaceutical companies monitor the safety of all of their products through their surveillance programs in which they collect, analyze, and report to the FDA spontaneously reported adverse experiences, and increasingly, because of international harmonization, we also undertake periodic reviews of all the safety data for better understanding of the safety profile of each drug.

In addition to what we do for every drug, there are occasionally areas of study that require more rigorous and systematic study. One of those areas obviously is safety of drugs in pregnancy. This slide presents some of

the points that we use within Glaxo Wellcome to help us, as we think about each new product as it approaches the marketplace, in determining when we should actually conduct a pregnancy follow-up study.

What will be the likelihood of first trimester exposure?

Will there be a potentially large exposed population of sexually active women of reproductive age?

Are there suggestions of hazards from animal data that we think translate into adverse effects on the human fetus?

Is the underlying medical condition itself a risk factor for adverse effects in the offspring?

Does the medication's mechanism of action give us some reason to expect an increased risk with this drug?

And again, the pregnancy category rating. We would be more inclined to pursue additional data for drugs that have an existing category C rather than a B labeling.

The example that I'll use is our completed study of acyclovir. I have to apologize for increasing the thickness of your binder in providing this extensive final report which tells you more than you ever wanted to know about acyclovir in pregnancy.

Acyclovir is a drug used to treat herpes simplex virus infections, and we established a registry, or

follow-up study, in 1984 because of the potential for wide scale exposure to a population of sexually active women of reproductive age and because of the background history of antivirals to that time which were less specific in their action and more toxic.

When the study was established, it was part of a broad epidemiology program that was looking at the general safety of acyclovir, so we were conducting a number of other studies using databases from health maintenance organizations and other approaches. This was also a joint effort with the Centers for Disease Control who had similar questions and were contemplating a similar kind of study.

Our objective was to monitor for risks of birth defects following antenatal exposure. And we naively thought in those days that we could use a hands-on intensive registry approach until we were able to conduct the same kind of study in an existing database, such as the HMO databases, and that never happened.

As we considered possible study design, we faced a number of different decisions. What were the exposures of interest? There were three formulations of the drug. We were mainly interested in oral acyclovir because that was the formulation used to treat genital herpes, but we didn't want to miss information about IV exposure which produces a much higher level of drug. But

we felt it was inappropriate to include topical acyclovir which is poorly absorbed systemically.

We made a conscious decision to look only at maternal exposures, not that paternal exposures were less relevant but were more difficult to study.

Our primary focus was on exposures during the first trimester of pregnancy despite the fact that the obstetrics and infectious disease community were primarily interested in us using these methods to look at the safety and efficacy of acyclovir when used in late pregnancy to prevent neonatal herpes.

As our outcomes, we were looking at the overall risk of major birth defects and we also intended to look at specific birth defects for any evidence of a pattern or cluster that might suggest that we could follow that up using a case-control study for more definitive study.

We recognize that many other outcomes could be interesting but were beyond the scope of our methods, and in fact we had the scientific rationale to pursue them at that point.

As we considered our objectives, we explored a number of different study designs. It was clear the cohort study was not ethical and a study using only a few sites to enroll patients prospectively would unlikely be successful because of the relatively rare outcome of birth defects,

especially specific birth defects.

A case-control study wasn't feasible at this point because the exposures in the population were too rare, and also we had no a priori hypothesis of the specific defect that might be associated with this exposure.

And we looked for existing data resources, and there were none available that could answer this question.

We therefore, determined to conduct an exposure registration and follow-up study in which exposures would be reported and included in our analysis only if they were reported prospectively before the outcome of pregnancy was known.

We needed some type of birth defect comparison group, and in this particular case, we chose the population rate because we felt that the primary exposed group was women with genital herpes who had no other a priori risks for delivering a baby with major birth defects over other populations.

And we chose the definitions used by the CDC and the Metropolitan Atlanta Birth Defects Program.

We also determined that other outcomes were beyond the scope of this approach.

The next slide attempts to depict how we determined which cases reported to the program would be

considered retrospective versus prospective. Any exposure that was reported after the outcome was known was considered to be retrospective, and that includes births -- and we received a lot of those -- as well as cases in which a prenatal diagnosis had confirmed the presence of a birth defect. So, we only enrolled throughout pregnancy those reports that were made to us before we knew the outcome of pregnancy.

At our initial data collection, we did a lot of learning in this process. We started out with a very ambitious approach, an 8- to 10-page data form that asked for every conceivable information on occupation, environmental exposure, all the drugs that were suspected to have some relationship to birth defects, and other potential confounders. And we quickly realized that if we were to obtain any useful data, we had to structure our data collection strategy in a very minimalist approach. So, we restricted our data form, as you can see in the binder, to a very limited set of information basically asking for exposure, timing, estimated date of delivery, prenatal testing, and depending on the registry, potential confounders specific to the individual drug or condition.

We also chose to collect basic information from a single reporter. We had many, many discussions with our advisory committee about how we might conduct long-term

follow-up through pediatricians, and we decided that our best approach, the most successful approach to maximize data collection would be to stick with the general reporter who called in the exposure, which was typically an obstetrician who was contacting the company through our drug information hotline for information about the drug in pregnancy. We felt that with using those reporters, they were more likely to be motivated, they were likely to have the relevant exposure and key outcome information which was major birth defects identified at birth, and that collecting information from them would not require additional steps such as gaining consent and contacting other providers.

In follow-up, we sent a form to the health professional at the estimated date of delivery, monthly reminders for 3 months after that if we didn't obtain information, and then used a last-ditch phone call or data form to try to minimize lost to follow-up.

The patient identifiers that we used to enable the reporting physician to identify the patient again at delivery -- not names, but it could have been a chart number, date of birth or initials -- were deleted at the completion of data collection.

We sent each of the reporters a thank you letter long after delivery with the encouragement to report

to us other exposures and also as an attempt to solicit other outcome information they may have become aware of for the infant involved in the exposure.

Targeted follow-up was conducted by the registry staff relating to specific birth defect cases, and that was based on a teratology review conducted at CDC, as well as questions from our own surveillance physicians.

In the analysis, we separate prospective from retrospective reports, estimate a birth defect risk, a proportion, from the prospective reports. And I'll show you an example in a minute. And we compared that risk against the expected risk, which varies depending on the study that we're talking about. We also evaluated all of the specific birth defects reported either through the prospective reporting or retrospective, and we analyzed those for patterns or uniqueness that might suggest a common etiology. And all of the data were reviewed by a multi-disciplinary advisory committee before releasing interim reports.

One of the challenges in trying to recruit exposures is getting the right message out. We really struggled with this in the early days of the acyclovir program. In trying to get the word out about the fact that we were conducting registry, we needed to avoid implying that we felt the drug should be used in pregnancy or that

we were suggesting that we think there's an increased risk when, in fact, neither was true.

We looked at a number of options for obtaining information, including referrals from different groups, scientific meetings, and I have to say that one of the most successful things we did was to include information in the package insert.

Sources of calls and referrals come from a variety of sources. The key point I wanted to make here was that our registries have tended to be international. So, we've made use of the local operating companies in different countries and wide use of our intranet to make available information about our programs to try to educate people in our local operating companies to increase awareness in reporting of these exposures.

Each of our programs has an advisory committee that helps in the review of data and also is another way of trying to disseminate information and encourage reporting in the sectors that they are a part of.

This next slide shows the data from the acyclovir registry. What I'd like to show is that of those reported cases over 14-plus years, we had a total of 1,246 pregnancies with outcomes known. Of those, 756 involved first trimester exposure to oral or IV acyclovir. When we calculate the risk of birth defects among first trimester

exposures, we look at the number 19, which is the outcomes of birth defects. That includes live births with birth defects, as well as prenatally diagnosed birth defects that may have not advanced to delivery. So, our nominator is 19 birth defects over a denominator of 19 plus the live births without birth defects, the 577, excluding the spontaneous and induced abortions.

So, we calculated a proportion of birth defects of 3.2 percent with a fairly tight confidence interval and compared that with a proportion from all exposures across all trimesters and concluded that when we compared this with the general population rate of about 3 percent, that our experience does not differ from the general population.

In addition, when we looked at our overall sample size, we concluded that regarding individual birth defects, that we had 80 percent power to detect a 7-fold increase in the risk of a birth defect that occurs in the general population with a rate of 1 per 1,000.

Our conclusion from study was that there were also no patterns among the birth defects to provide a signal of potential common etiology. We certainly need to recognize the potential limitations, which include under-reporting of exposures, under-reporting of birth defects, the inability to identify all birth defects within the first year of life, potential differential reporting, and

losses to follow-up.

But despite these limitations, we felt that the information was useful in the course of counseling women following inadvertent exposure. And in terms of the value of this study, the greatest benefit clearly was that more information is available for patients and their providers.

It was clearly useful to our company in our evaluation of safety of this medicine. It taught us a lot about how to do these studies. We were able to include this general information in our product label, changed the labeling category from a C to a B.

And the information was also useful as the CDC developed their sexually transmitted disease treatment guidelines relating to genital herpes.

We participate in a number of pregnancy follow-up studies looking at a variety of medications, and let me just highlight that we're involved in two studies, the antiretroviral registry and the North American Antiepileptic Drug Registry, that are multi-company collaborative projects. The AED pregnancy registry enrolls women themselves, rather than enrolling through physicians, and the antiretroviral registry, which is managed by PharmaResearch is a registry looking at 14 different products of 8 companies.

Let me turn to some of the lessons that we've

learned from just practical experience over the years in trying to conduct and improve these kinds of studies. I'll take these five points in order, but first of all, let me mention that these are all very labor intensive studies that require numerous attempts to contact patients or physicians for very limited amounts of information.

So, as we decide how to study any hypothesis relating to drug safety, we clearly must balance the ideal study design against the probability that we'll actually obtain useful data. If we build a perfect study, will the study population rise up to enroll, provide years of intensive follow-up information? Probably not if we're talking about a hands-on study.

We must also tailor the design of our study to the specific question at hand and not ask one design to answer all possible questions of potential interest. For many drugs, the first level question is, is this drug associated with an increase in major birth defects? If that's the question, then some variation of a basic approach makes sense.

However, if the question is what's the likelihood that this drug causes a specific defect -- and we've had examples. One example was a drug that's widely used, and there was a signal of a possible relationship with a very rare abdominal wall birth defect that occurs in

about 1 in 10,000 pregnancies. Clearly we would not set up a prospective study to evaluate that. We'd conduct a case-control study, which is underway I think.

If we were looking for subtle defects or delayed effects way beyond birth, we'd certainly not select this basic design for a registry. But if we're looking for the general margins of safety, some variation of a basic approach might, indeed, be tailored to meet the needs of a particular medication. So, it's critically important to select the right method for the outcomes of interest.

I'd like to make another point, which is that some outcomes like spontaneous abortion and maternal outcomes may occur more commonly than overall, certainly, specific birth defects and require a different type of study design, different amount of data, different types of data, and would be very difficult to squish that into the context of one of these studies looking at birth defects.

So, the optimal method really needs to consider two dimensions that often work at cross purposes in a hands-on prospective study and those are sample size and study complexity.

A large sample size may be obtained best by using a very simple approach and that may be appropriate for these studies of major birth defects.

Studies requiring more complexity or a multi-

step design will have extreme difficulties in attaining a large sample size and will require enormous resources and may, even with enormous resources, not be able to achieve its objectives. Those would include studies of delayed effects.

Success of recruitment in the follow-up is also dependent on study simplicity. There are providers and patients who elect to contact a registry and provide information. The patients and physicians who do come forward are still only a small sample of the exposed populations, but I take as my 100 percent starting point the people we do find out about.

Retention is a major concern. Among the total population, we can look at the effects of different levels of complexity and study design. If patient consent is required in order to obtain additional data from the patient or to be able to go to a number of different providers for different kinds of information, the participation rate will be significantly lower, and anecdotal evidence suggests that it might be 50 percent.

Other exposures are lost when referrals are required. For example, if a physician must ask a patient to contact a registry, the patients who are intimidated by the health care system may not actually be referred.

As duration of follow-up is extended, then the

likelihood of obtaining complete information is further diminished.

The potential for lost information, selective information, must be considered, and this is not a trivial issue as we are talking about very labor intensive data collection. At best we'll still find ourselves with many cases that are basically irrelevant to the study question because the exposure occurred in an irrelevant trimester or the exposure was reported retrospectively. I can't emphasize enough the importance of trying to recruit exposures very, very early in pregnancy.

So, such a labor intensive method and imperfect method is fine because it still provides us with substantially more information than we would have otherwise. But it's fine as long as there are no better and more efficient alternatives. And I do think that it's within our 10-year horizon to realize the prospect of large linked databases to help in making this data collection strategy much more efficient and less dependent on active hands-on follow-up. The advantage of using an existing database is that all exposures can be identified. It's not dependent on voluntary reporting. Follow-up information is already collected. It's much easier to get back to the individual patient information should it not be in an automated database.

While these databases currently are not sufficient, because they don't have enough detailed information and they're too small, I think the movement is for automated medical records databases to be much more comprehensive including kinds of information that we'd really like to see like LMP dates, that we might be able to see over the next 5 to 10 years that consolidation across multiple databases might be able to be a helpful addition and keep us from having to reinvent these kinds of hands-on studies again and again. But, of course, those will still probably not take the place of case-control studies which remain a mainstay in being able to test hypotheses that arise.

Let me highlight three issues that I think must be addressed if we're to move forward in the kinds of registries that we're talking about today. One is the issue of consent and IRBs. Those of you who know me know this is a pet issue for me. I'm very concerned that the evolving legislation, HHS regulations, and practice guidance that's being developed in many sectors is moving in a direction that may, in fact, stifle our ability to conduct this kind of research by requiring informed consent and perhaps putting some constraints on our ability to do this research which, in effect, may help us to conspire against collecting this kind of information. So, I think

it's very important that we stay tuned to the evolving policy development and have our voices known so that we don't find ourselves unable to study these issues.

You've already heard the comment about adverse event reporting, and clearly we need some clear guidance with the FDA about how to report events that emerge from these kinds of studies. Our preference is to use study guidelines rather than the spontaneous event guidelines. This lack of clarity creates a significant barrier when multiple companies are collaborating on a single study.

And there needs to be greater understanding of how information coming from these kinds of studies can be used and how they should be interpreted. The public and providers are a bit in the dark. We need ways to disseminate this information in ways that are helpful to providers and women who are pregnant or considering pregnancy in the face of enormous pressures that suggest that any exposure to any medication will be hazardous.

So, let me stop there and see if there are any other questions. I could probably go on and on, but I'll stop there.

DR. GREENE: Thank you.

Questions for Dr. Andrews, please. Jim.

DR. LEMONS: That was very interesting data. I had a couple of questions related to the acyclovir study to

see if there were any other conclusions you could draw. One is, do you have any estimate of what percent the prospectively followed cohort represented of all pregnant women that might have been exposed?

Secondly, do you have any data from that study or other studies that would reflect upon the quality of evidence that might be collected from a retrospective sampling? That is, do you know, in fact, that the retrospective sampling, looking at least major birth defects, would have been inaccurate or misleading?

DR. ANDREWS: Good questions. The first question. We tried many times to estimate the total exposed population, which requires understanding the use of the drug and making some estimation of fertility in women with genital herpes, and we had very wild estimates. I think our bottom line is that we know that we only captured a fraction of the exposed population, and how big a fraction I really don't know.

Your question about retrospective reporting. It's very clear that when people have identified an outcome and want to tell us about it, there's a reason. So, there are a number of providers who are very interested in using acyclovir to prevent neonatal herpes. So, they pick up the phone and call us routinely to tell us how safe the drug was, and we have no idea how representative that experience

was. It's clearly not.

DR. GREENE: Ken?

DR. JONES: Elizabeth, I'd like to make a comment and also ask you a question. It relates to one of your slides here on design considerations. First of all, you say that cohort studies are not feasible because outcomes are too rare, and I agree with you on that if what your outcome is is single major malformations, which you clearly make as your outcome.

However, I think as many of us believe -- clearly not all of us because I know Allen Mitchell is down there.

(Laughter.)

DR. JONES: But I think as many of us believe, human teratogens are primarily associated with a pattern of minor malformations as opposed to a single major malformation. So, I would take exception to the issue that outcomes are too rare because I think when one is looking at minor malformations and patterns of minor malformations, you can do this with much smaller numbers. And that's the first point that I'd like to make.

Now I'd like to ask you a question, and that relates to your comment that cohort studies are not ethical. Could you explain to me what you mean by that?

DR. ANDREWS: Simply that we felt at the time

that acyclovir was being introduced in the mid-1980s, that trying to enroll women prospectively, we would not be enrolling them in a clinical trial to expose them intentionally to acyclovir, and it would be very difficult to, through a set number of centers, identify those with inadvertent exposures.

DR. JONES: Okay, well, that may be true with acyclovir, but I think that there are many drugs that are being marketed that women are taking today that inadvertent exposures are relatively frequent, and if we are looking for outcomes again other than major malformations, in particular, if we are looking for outcomes in terms of neurobehavioral development, which I think is a critical issue as far as this is concerned, which has to be determined at 4 to 7 years of age, we have to be enlisting mothers as opposed to obstetricians in terms of the individual that we're talking to. Therefore, we have to be going to IRBs and we have to be getting consents of mothers to allow us to evaluate their pregnancies, their newborn baby, and then follow their baby up through 7 years of age. I don't think this is unethical. I think this is very ethical.

DR. ANDREWS: And I would completely agree with you. I would say on my little diagram with study sample size and complexity, that is over there on the high end of

complexity and, fortunately, requires a smaller sample size because that would be extremely difficult to do for hundreds or thousands of exposures. Absolutely agree.

DR. WISNER: My question is about exposures. As a clinician, as I listened to the information, I'm wondering how generalizable it is to the patients that I see in my office. So, for example, for this study for acyclovir, would exposure mean that patients who were included who perhaps had a dose or two, found out they were pregnant, and discontinued, as well as patients who perhaps used the maximum dose for an extended period of time? So, my question is whether you could comment on your experience with creating operational definitions of exposure and how you could present that kind of information to clinicians who have to use the data?

DR. ANDREWS: We struggled with that, and we used a variety of approaches. The most complicated approach was to actually pictorially describe every single case with a graph of every week during pregnancy, and we've actually put the exposure time, as best we could infer from the reports, and dose and indication. That for hundreds of patients became incredibly too detailed. We felt that clinicians would like to be able to refer to something like that, and in fact, I think it turned out not to be that useful.

We used a variety of other ways of looking at dose, indication, duration of therapy, and that's going to be a different issue for every particular drug.

So, I guess one answer to that is when people called for information, we could actually refer to specific information in the cases.

DR. GREENE: Are there any other questions for Dr. Andrews?

DR. ANDREWS: Let me just add another comment. Most of the questions that come in to these hotlines aren't that specific.

DR. GREENE: Thank you.

The last scheduled speaker for the morning is Dr. Evelyn Rodriguez. Please.

DR. RODRIGUEZ: Good morning. I want to open up by saying that this guidance was really drafted by a large group of dedicated individuals, part of the Pregnancy Registry Working Group. Carolyn McCloskey, an epidemiologist on my staff, worked on this document, along with Sheila Weiss, who is on the committee today, Jean Manson and others who are too many to list this morning.

The guidance was drafted by this committee and then published in the Federal Register in June of 1999. You have a copy of the draft and the comments that we received regarding the draft in your background package.

What I'd like to do now is to bring you up to date on the agency's current thoughts in preparation to seek your advice on how we proceed toward finalization of this document. I think PhRMA and others who have submitted comments will recognize that we've incorporated many of the concerns into our current thoughts.

This is the outline of what I'll be covering today. I'm going to be discussing the agency's reason for drafting a guidance document to industry, describing what a pregnancy registry is. Every registry needs a protocol, so I'll be talking about the purpose of establishing a protocol, and a little bit about the registry study design, touching upon recruitment, considerations in reporting source, issues regarding follow-up, comparison groups that can be used, issues in data analysis, and finally reporting results.

Why a pregnancy guidance document? Well, the agency felt it was important to provide useful data to health care providers in caring for their patients. Clinicians really have a dearth of data to refer to regarding issues arising in the use of drugs or medical products during pregnancy, and because those data are lacking, we felt it was important to address it in a guidance document.

Well, what is a pregnancy registry? I'm going

to use the S word. A pregnancy registry is a study and it could have many, many designs. There's not a cookbook approach that one can use to design a pregnancy registry. Often it's hypothesis generating if the risk is unknown. It could be hypothesis testing if, for example, animal studies point to a particular possible adverse outcome of concern. The design would depend upon the hypothesis and outcomes of concern, and ideally prospective enrollment of subjects would be actively pursued. It also would outline how information will be collected in a proactive manner for providing the scientifically based outcome data that's needed.

What is the purpose of a pregnancy registry? Well, we need to determine the risks associated with drug use during pregnancy, and we need to provide a measure of this risk and, whenever possible, to determine the risk factors associated with the adverse outcomes. Very importantly, as Sandy had described earlier this morning, we need to put our arms around the margins of safety regarding either risk or lack of risk.

We have limitations of current data resources. We have population-based surveillance systems, and what I'm referring to is Medicaid, automated databases, HMO-based automated databases. But presently there's no easy linkage of maternal exposures that we can connect to fetal outcome.

Spontaneous reports, just by virtue of what they are, are biased in the kinds of reports that are received and no incidence rate is available.

There is a lack of meaningful data available in clinical trials because all of us know that women are specifically excluded from these trials and that once women become pregnant in these trials, they're frequently terminated or excluded from this trial.

What is the purpose of a pregnancy registry protocol? Well, the protocol should assure the quality and the validity of data elements that are going to be collected and should assure the documentation and consistency of the research methods.

Registries are observational, nonexperimental studies that actively enroll subjects. The registration is ideally prospective as early as possible in pregnancy, especially if the outcomes of concern are impacted upon early in pregnancy, recognizing, of course, that drug exposure can be anytime prior to pregnancy or during gestation.

One should determine rates of outcome among mothers exposed to the drugs and one should consider the use of comparison groups. The easiest is to use known background population rates, but one can also consider concurrently enrolling unexposed mothers with or without

the underlying disease of interest.

Baseline information should be carefully collected at enrollment that can be risk factors for the outcome of interest, and the focus should be on the enrollment of prospective subjects who are enrolled during pregnancy when there is an unknown fetal outcome in order to provide the unbiased type of risk estimate.

Retrospective subjects, although not part of the prospective analysis, can be collected to develop a case series and a description of these cases reported to the registry. These, of course, would be subjects who are enrolled or information obtained after the outcome of pregnancy is already known.

Another consideration in design of a pregnancy registry is the consideration of the feasibility of successfully completing the study. One should anticipate the patterns of drug use or product use relative to fetal development, and one should specifically have case definitions in mind and have a method for the identification of those adverse outcomes specifically delineated in the protocol.

What products are good candidates? Products, if they're used frequently where inadvertent exposures are apt to occur, should be considered, and products initiated or continued during pregnancy as therapy.

Also, when available information suggests a need, such as a concern about a pharmacologic class, concerns that arise because of animal reproductive data, any chemical structure/activity relationships that one is concerned about, or when isolated human case reports lead to a concern.

When in a medical product's lifetime should a registry be established? It should be established when the need is perceived, either at the time of approval, which we hope would be most likely in the future, or possibly with a new indication for a specific medical product, and when a post-marketing signal is observed.

What are the elements to consider in the pregnancy registry design? Well, the protocol should assure consistency in data collection and analysis, and we would encourage industry companies to consult FDA in the design.

The background section in the protocol should outline the animal reproductive toxicity studies and any concerns that have arisen because of those studies. They should cite relevant pharmacologic and toxicologic studies and any human experience from spontaneous reports or earlier human studies and should also provide an estimate of risk in human pregnancy in order to guide the sample size and power issues.

The research methods should carefully outline patient recruitment which hopefully would consist of very proactive enrollment strategies and clearly outlined follow-up plans. Any drafts of registry announcements should be included as well, such as informational pieces containing contact telephone numbers and website addresses, and the product label should contain the contact information as well.

Announcements may appear in professional journals, women's magazines, professional and maternal/infant advocacy group newsletters, Internet sites, mailings to specialists, lectures, and informational booths at professional meetings.

However, unless specifically approved for use during pregnancy, any recruitment effort should not promote the use of the product during pregnancy.

All product-specific promotional materials must be submitted to FDA at the time of first use, and review prior to use is not necessary unless the product was approved under expedited approval regulations.

The protocol should also include scripts that will be used in response to registry announcements and in order to recruit and enroll subjects. To increase awareness, sponsors are encouraged to work with FDA, CDC, the Organization of Teratogen Information Services, the

March of Dimes, and others who have interest in this area.

The FDA plans to develop a website page that will list known pregnancy registries as well.

With regard to research design and reporting source, there are several sources of information that one may use. One may use subjects in obtaining baseline and follow-up information or health care providers, or both. Each has its advantages and disadvantages.

The use of subjects may minimize loss to follow-up and may facilitate multiple follow-up during pregnancy and also enhance the number of contacts and enhance the quality of infant data. It also would facilitate informed consent in the event that a medical record would need to be pulled in order to validate specific infant outcomes. But it may be more expensive because there would be more frequent and extensive follow-up. However, that would need to be balanced with the loss of follow-up that can be expected in a registry study.

Health care providers are a convenient and good source of medical data. It's a very economical way of collecting data and may require fewer contacts. However, data collection on maternal and infant events may be incomplete, especially if these are obtained mostly from obstetricians or family practitioners who may not follow the infant and may lose track of the infant after the child

is born. And loss of follow-up may be substantial because, frankly, busy clinicians are busy and this is not going to be on the top of their priority list. So, they may not be as motivated as perhaps individual subjects.

Patient follow-up. Of course, these plans would need to be guided by the outcomes of interest, and the challenge, as Elizabeth noted earlier, is to balance the quantity of the data along with the quality of the data. Follow-up plans should outline and describe the follow-up procedures in the protocol.

It should update drug exposure and risk factor information and obtain results of any diagnostic tests when these are available.

It should plan on collecting information if these are available, on spontaneous abortions, elective terminations, and the medical reasons for these events if these impact on the outcomes of concern of the study.

There should be consistent, standardized, similar follow-up for all women in order to avoid bias.

And criteria should be prespecified to define subjects that are pending versus those who are lost to follow-up.

Considerations for prespecified, standardized case definitions for all outcomes should be made, and these can include, depending upon the outcomes of interest again,

on maternal, labor, and delivery events, major categories of anomalies, developmental effects, and so forth. One should try to confirm as many of these outcomes as possible, perhaps by accessing autopsy and pathology results, birth and death infant records, expert evaluations of the infant, and perhaps long-term follow-up depending upon the focus of the study. Again, the feasibility of obtaining all of these outcome data needs to be considered.

One should define the outcomes of concern and hypothesis and define the characteristics of the exposed population that one is expected to enroll. One should have some information and define the biological impact of the treated underlying medical conditions upon the adverse event being ascertained and describe what is known about drug exposure during pregnancy. One should be able to anticipate the likelihood of discontinuing the treatment upon the diagnosis of a pregnancy which would, of course, impact on enrollment and follow-up considerations.

In the selection of comparison groups, one can try to enroll women who have the underlying medical condition or women who are exposed to a similar product for the same indication or perhaps use multiple comparison groups. But we recognize that the easiest comparison group to use is known background rates that are already published and available.

Statistical considerations include having an adequate sample size to address the hypothesis of concern if a hypothesis is postulated, to estimate the risks of suspected outcomes of scientific interest, and of course, estimate the power to exclude certain levels of risk.

In the data analysis, as Elizabeth pointed out earlier, prospective and retrospective cases should be separated. Pregnancy outcomes and fetal abnormalities should be described and looked at very carefully. The subjects lost to follow-up should be compared to the subjects who continue to be enrolled in the study to see if there are any issues with possible bias.

In a cohort design, one should calculate a point estimate and 95 percent confidence intervals which would help us our arms around levels of risk, and one should compare these levels then to population background rates.

Well, registry reports, I'd like to address, are considered information derived during active solicitation of information from patients. So, I think PhRMA and the companies are relieved that FDA is now a little bit clearer about what the reporting requirements are. We took that comment very much to heart and wanted to provide clarity to encourage registries to be developed.

So, as such, they should be handled as safety

information obtained from a study as the 1997 guidance which PhRMA had referred to earlier. I do want to highlight the fact that FDA post-marketing safety reporting regulations are in the process of being updated, and so considerations of registries and reporting requirements will be considered and part of those safety regulations.

Additional information in the registry guidance includes references that were used in developing the guidance. We also developed a long laundry list of elements for possible consideration in pregnancy registries knowing full well that this is just a laundry list from which companies and persons involved in a research design can select from depending upon what the outcomes of interest are. Also sample size determinations by specific adverse pregnancy outcomes are also included in the document.

Thanks a lot. I think I'm humbled by the previous speakers before me and would like to now entertain any questions regarding the guidance document.

DR. GREENE: Questions for Dr. Rodriguez, please? Jan?

DR. FRIEDMAN: I'd like to make a comment and ask you a question.

First, the comment returns to one that both Allen and I made before. I don't really understand why the

default position would be that there should not be a registry for a drug unless there's some reason to think that there's concern because I don't think we know when there's reason to be concerned. It seems to me a more reasonable position would be the default position should be there should be a registry unless there's clear indication there's no need for one, for example, the drug isn't absorbed, a topical that's not absorbed. That's the comment.

The question is it seems to me that part of the reason that both you and Dr. Andrews see the difficulty of collecting these data, the detailed data, has to do with where you're sitting. If you're actually taking care of patients, most of these data are available. Babies are examined. There are sort of routine developmental evaluations, maybe not detailed, but there is information that's available.

When information is gathered on animal studies, there's some cost in obtaining the data from the animals, and it seems to me if you weren't just depending on voluntary compliance, asking, begging people to provide information, it might be easier to get it if you were to develop a system where someone like Ken Jones was encouraged to actually look at some of these babies and gather the data that you need and provide them to you in a

reasonable fashion. You might find that the quality of the data and the detail of the data and the ability to get these syndromes and some of the things that we want to look for would be a lot easier.

Would you like to comment on that?

DR. RODRIGUEZ: I think your point is well taken. As I had mentioned, the design of a registry would really be predetermined by the outcomes of interest. So, it would be very important, though, to be very careful in the data collection that one performs to do it in a very standardized manner. So, one may not be able to cast a wide net and try to solicit information from every possible source. Perhaps some targeted study is needed depending upon the outcome of interest. For example, if it's a developmental delay question or a behavioral question, that may be handled in a more focused study as you just described.

Does that answer your concern? Certainly you'll have a chance to discuss this when the committee convenes to talk about the questions that we posed to you.

DR. GREENE: Lew?

DR. HOLMES: Evelyn, I have one question and one comment.

The question. I run the AED pregnancy registry. It would be very helpful to us if the guidance

document said a registry can report adverse outcomes every 6 months just as a matter of fact rather than now where it's up to the individual company and we've been given the option of having the companies apply for permission to do it every 6 months. But it would be a lot easier if you just made it a priori when you have a registry that meets certain guidelines, this is then automatic. It would save an enormous amount of personnel time.

The second point concerns this follow-up question that Jan is speaking to. We have a hospital-based registry. We talk to the mother. We get her consent to request information from the doctors, and what he's talking about is certainly obtainable if you're willing to provide the support for the personnel that walk through that. It's not the same as having Ken do the exam, but it's a more efficient system when you're covering a large geographic area.

I'm not convinced any existing database is an adequate control, and what we're going to try to do, if we get enough money, is to start the process of trying to recruit controls which, as you might guess, is not going to be automatic or easy or we know exactly what to do. Because I really think a registry, where you're asking a woman to make a phone call is different from any database like the CDC database or any other that has a totally

different design.

So, I'd say, as we talk about pregnancy registries, I don't think you can just accept a priori that you can use historical controls. I think quite the opposite. The data is going to be much more believable if you have intrinsic controls.

DR. RODRIGUEZ: I'd just like to address one thing you said in your statement regarding expecting women to call up and make reports. I think it would be much more useful for designers of these registries to actually call up the subjects rather than relying upon the subjects to call in to the registry to make a report. That would allow for more standardized collection.

DR. HOLMES: You don't deal with IRBs. An IRB would never accept that.

DR. RODRIGUEZ: Is that right?

DR. HOLMES: Automatically step number one, part of the consent process is she has to pick up the phone. I can tell you as someone who is convinced I'm a great persuader of a lot of women to call this number, I know they don't. So, it's one of the rate limiting steps in a pregnancy registry. She is actively doing it. Fewer shes do it, but the lost to follow-up rate is less than 5 percent. So, she's engaged.

DR. RODRIGUEZ: Right, understood. However,

once a woman is enrolled in terms of obtaining follow-up information, I think what we're encouraging is that instead of relying for the woman to make a phone call to provide follow-up information, that the study would call the woman in order to obtain the information, as is done with providers, I would imagine.

DR. HOLMES: Sure, as long as it's part of the consent process.

DR. MONTELLA: You can get consent up front to call patients, though. You have to get it up front for everybody. Particularly in pregnancy, everybody registers very early on. Many people register early on. Some people don't come at all. But those that do, you can get consent up front to make a phone call. It's a very specific consent: Is it all right to call you? You can do that.

DR. GREENE: Yes, please.

DR. WEISS: I'm a little concerned because you were the third speaker this morning that talked about maybe not using concurring controls. I agree with Dr. Holmes there that if you don't get some sort of comparison group that's enrolled in a similar manner to the women you're enrolling, then you're losing the critical information that you really need to make a risk assessment.

I started looking at this in the literature and found that the rates of spontaneous abortions in women who

enrolled in these registries is about half the population rates because of the way that they are enrolled and even perhaps because of what their risk might be.

Also issues about therapeutic abortions, if the drug causes anomalies and they're discovered early, the people taking the drug might have higher rates of therapeutic abortions. You won't know that unless you have a comparison group from a similar population and be able to make that comparison.

I think the lack of comparison group is one of the reasons that prior data has not made it into the label because you don't have that thing to compare them to to understand what your results really mean. And I urge you and the committee working on this to really think about this issue before you agree that that's a valid design, not to have a comparison group.

Thank you.

DR. GREENE: Other questions or comments?

(No response.)

DR. GREENE: Well, I think we're right about on time, and I think we will adjourn for one hour for lunch please.

(Whereupon, at 12:01 p.m., the subcommittee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:12 p.m.)

DR. GREENE: We'd like to reconvene, please.

This afternoon our first task is to address some of the questions that the agency is posing to the committee. Before we address the questions that are formulated for us in our agenda packet, I would like to take a minute or two to ask a few questions of my own. I will take the prerogative of the chair to do that.

As I reviewed the responses of various sponsors and industry to the draft guidelines, I thought that there were several themes that came though, and I'd like to address some of these themes first before we get straight to the questions as proposed in our agenda books.

The first is recognizing the preponderance of academicians around the table and the preference that everyone would have for the perfect study, I would like to ask whether it's necessary really, for the kinds of information that we want to glean from registry data, for the sponsors to enroll contemporary controls. It seemed that that was a consistent theme in the objections of industry to the draft guidelines, that they thought that was unduly and inappropriately onerous. And the question is, is that really necessary? I'd like to open that question for discussion for starters. Lew?