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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE

PUBLIC MEETING

Monday, October 18, 1999

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The Ballroom
2 Montgomery Village Avenue
Gaithersburg, Maryland

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JAYNE PETERSON

C O N T E N T S

Morning Session

C O N T E N T S (Cont'd)

P R O C E E D I N G S

CHAIRMAN AZZIZ: Good morning. I'd like to begin this morning's session. This is a meeting of the Advisory Committee for Reproductive Health Drugs. I'm Dr. Ricardo Azziz. I will be chairing the morning--the committee meetings.

I'd like to first ask the members of the Committee and staff, to introduce themselves, and then we will proceed onto more formal introductions and sections; beginning--I'd like to remind you to press the button. There's a new tactic.

DR. HOUN: I'm Dr. Florence Houn. I'm with the Office of Drug Evaluation III, the Office Director.

DR. KWEDER: I'm Dr. Sandra Kweder. I'm the Office Director for Office of Drug Evaluation IV, and I'm also one of the co-chairs of FDA's Pregnancy Labeling Task Force.

DR. RODRIGUEZ: I'm Dr. Evelyn Rodriguez, and I'm from the Office of Post Marketing Drug Assessment.

DR. RARICK: And I'm Lisa Rarick. Good morning. I'm the Director of the Division of Reproductive and Urologic Drugs.

DR. BENNETT: Reggie Lee Bennett; Medical Officer, Division of Reproductive and Urologic Drug Products.

DR. HARRIS: Joseph L. Harris; from King-Drew

Medical Center, Los Angeles.

MS. SCOTT: Julia Scott; National Black Women's Health Project, Consumer Representative.

DR. DATTEL: Bonnie Dattel, Maternal and Fetal Medicine, Eastern Virginia Medical School.

MS. PETERSON: Jayne Peterson, with the Advisors and Consultants Staff and CEDR.

DR. FALK: I'm Richard Falk, head of Reproductive Endocrinology, Columbia Hospital for Women.

DR. LERNER: I'm Jodi Lerner, from Columbia-Presbyterian Medical Center in New York.

MS. PAULS: I'm Lana Pauls, ASsociate Director for the Division of Reproductive and Urologic Drug Products.

DR. GREENE: I'm Mike Greene, Maternal Fetal Medicine, Massachusetts General Hospital.

DR. TRUSSELL: James Trussell from the Office of Population Research at Princeton University.

DR. CRAGAN: I'm Jan Cragan from the Division of Birth Defects and Development Disabilities of CDC.

DR. WEISS: I'm Sheila Weiss, Epidemiologist with the University of Maryland Schools of Pharmacy and Medicine.

CHAIRMAN AZZIZ: Welcome this morning. I would like to remind the committee and those attending that the purpose of this meeting is to provide a guidance to the Division on the Development of Draft Guidances for the FDA

reviewers regarding pregnancy outcome, pregnancy registers, and estrogen labeling.

I would also again like to ask you to speak into the microphone. You have to press the button, and then somebody else has to release you to allow you to speak, so it may take a few seconds before you do that.

We're going to try to stick on time--to our time schedule. In fact, we may try to allot more time for the afternoon session, so for those who are involved in the afternoon events, if you can just be here a little bit earlier than before.

Without further ado, I'd like to introduce Dr. Lisa Rarick, Director of the Division of Reproductive and Urologic Drug Products.

DR. RARICK: Thank you, Ricardo. And good morning, everybody.

I'm going to start my comments from here, and the next part where I'll speak I'll come to the mike. But for now, I just wanted to make some brief comments about today's agenda.

As Dr. Azziz mentioned, there are several things on our agenda. I wanted to point out to both the committee and participants, we have three sessions of open public hearing currently scheduled. We do not have to use them all, but we know that we will be using at least two.

Just to clarify why that is true, the first session of open public hearing is planned for the beginning of the morning, right after my comments, and that's for any general topics that aren't' necessarily on the agenda, or for people who have comments on Today's agenda issue's but can't stay to those sessions of open public hearing.

There will be an open public hearing right after the discussion of pregnancy labeling and registries, and how they impact our division, and then there will be an open public hearing session about estrogen replacement therapy which has been planned for the afternoon.

As Dr. Azziz mentioned, we have a lot of guidance documents that are different stages of development in the agency. The ones we'll be discussing today, you'll be hearing about quite substantially, and after the first open public hearing I'll go through a little bit of explanation of what is a guidance document, to make sure we're on track.

I'd like to remind those who are going to speak in the open public hearing to please identify yourselves and your affiliations when you do come to the microphone.

Later in the day we'll discuss a couple of administrative issues with the committee about two subcommittees that exist for Reproductive Health Drugs Advisory Committee. I wanted to make the committee aware of those subcommittees and find the interest level in

participating in some of those other discussions.

And that's it for my opening, Ricardo.

CHAIRMAN AZZIZ: At this point I'd like to introduce Jayne Peterson, Executive Director of the Advisory Committee for Reproductive Health Drugs. She'll discuss waivers and membership.

MS. PETERSON: What I'd like to do is read the waiver statement for this meeting.

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

"Since the Committee's discussion will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to entire classes of products, in accordance with 18 U.S.C. 208, general matters waivers have been granted to all Committee participants."

"A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30, Parklawn Building."

"In the even that the discussions involve any other topics 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."

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

Thank you.

CHAIRMAN AZZIZ: Just a point of information--Drs. Lerner, Trussell and Greene are noted as "Consultants." They are joining the Committee later in the week. But for the purpose of the meeting, they are consultants.

At this point, I'd like to open the session for Open Public Hearing. I would like to note that the purpose of this first Open Public Hearing is to allow anyone to speak on any general topic, even not related to this meeting. And we don't have anybody noted to speak on any subject yet. Is there anybody present that would like to make general comments.

[No audible response.]

Without any member desiring to speak, let's move on, and Dr. Rarick has some introductory comments. She's already up at the podium.

DR. RARICK: Thanks, Dr. Azziz.

As I mentioned, we're going to be discussing several guidance documents today. Some of them are actually

new, de novo documents, and some of them are old documents that are being revised.

In the arena of pregnancy labeling and registries, there are two draft guidances that are new issue guidance--the guidance documents that have been out for comment, and are now back as somewhat implementable guidances--and we'll be hearing about those this morning.

The purpose of bring those to this committee's attention is to, one, let you know that such guidances exist and that there's a lot of thought on pregnancy labeling and how to implement pregnancy registries appropriately in the agency. And at the Division of Reproductive and Urologic Drugs, we'd also like a lot of comment from you all about how those guidance documents might impact our drugs.

Later in the agenda we'll be talking about horomone replacement therapy. There are two somewhat old guidance documents, called "Estrogen Class Labeling," and "Hormone Replacement Therapy Drug Development Guidance Documents," which are in the process of modification, and require a lot of input from the experts around the table and the public, who will be here, I'm sure, of give us some advice regarding those documents.

Why don't we talk for a minute, though, about what a guidance is, so that both the committee and those present are aware of the concept.

There was, in 1992, a Federal Register notice about good guidance practices. This resulted after years of discussion about how the agency might be more appropriate in its guidance development, implementation and also imposition on either industry or FDA.

The "Good Guidance Practices" document set forth general policies and procedures for developing, issuing and using such guidance documents. The purpose was to help ensure that agency guidance documents are developed with adequate public participation; that guidance documents are readily available to the public; and that guidance documents are not applied as binding requirements--and that's a very important point. They are not binding requirements.

The purpose of them is to provide assistance to the regulated industry by clarifying requirements that have been imposed by Congress, or issues in regulations by FDA, and explaining how industry may comply with those requirements. We also use guidances to provide specific review and regulatory and enforcement approaches to help ensure FDA's employees implement agency's mandate effectively, fairly and consistently.

The term "guidance documents," includes documents prepared for FDA staff exclusively, or prepared for applicants or sponsors, or prepared for the public, that relate to the process, content and evaluation or approval of

submissions; that relate to the design, production, manufacturing and testing of regulated products; or describe the agency's policies or positions or approach to a specific issue; or establish inspection and enforcement policies--and we won't be going into that today.

They don't include internal discussions, or internal FDA procedures and policies.

In terms of legal effects, I mentioned they are not binding. Guidance documents do not themselves establish legally enforceable rights or responsibilities. They are not legally binding on industry or the agency; rather, they are explanatory. They explain how the agency believes statues and regulations apply to certain regulated activities.

A sponsor or the agency may think of alternative methods. Alternative methods that comply with relevant statutes or regulations are definitely acceptable. If a company or person wishes to choose an approach other than that set forth in a guidance document, FDA will entertain and discuss with that company or person alternative methods. We encourage industry to discuss alternative methods with the agency before implementing them.

So, again, you'll be talking about guidance documents. In terms of the process of guidance-document development, when we have--in the arena today we're only

talking about a certain type of guidance document, which requires public participation and public input prior to finalization. In that case, the agency generally develops a draft guidance document, publishes that--the notice of availability--in the Federal Register, and publishes on our Web site; allows a certain period of comment; entertains comments; evaluates comments; and either then finalizes a guidance document, or puts it out again for comment. And we'll see how things go with your comments today as to where we are in the process for many of our guidance documents.

Next slide. We're going to hear this morning about pregnancy labeling and pregnancy registries. We have an FDA internal task force, headed by Dr. Kweder, who will be speaking with us about their review; an update on the status of pregnancy labeling.

We also have a guidance document out about--a guidance to industry about pregnancy registries, and Dr. Rodriguez will tell us more about that.

Next slide. How does that relate to the Division of Reproductive and Urologic Drugs? As you can imagine, there are--the bulk of OB/GYNS in the agency do sit in the Division of Reproductive and Urologic Drugs, so we are often asked to comment on pregnancy labeling and pregnancy registries issues throughout the Center.

It actually is not that simple, because in our own

division we don't have that many instances where there are lots of questions about pregnancy labeling and registries. For example, there's a lot of information on contraceptive hormones and effects of first trimester and other exposures. In our menopausal drug groups, we don't deal with pregnancy. Benign GYN is one area where there are some questions about how to treat--in terms of drug development and reproductive-age women, and how we would handle pregnancy outcome questions.

Again, in our urologic drug side, there's rarely the need to look into pregnancy labeling or issues, in terms of prostate disease, as that is a male indication; male erectile dysfunction, incontinence and bladder disease, though, is an area where there may be some need for further thought on the Division's part about imposing pregnancy registries.

Today, we're going to ask Dr. Bennett, as you'll see from the agenda, to discuss with us infertility therapies, and whether or not the Center, and this division, knows enough, or needs to know more, or are there ways to get more information about pregnancy outcomes and use of infertility therapies. There are lot of points to consider. I'm sure Dr. Bennett will bring them to your attention also, but I'd like for the Committee to remember the complexities of protocols used in infertility and assisted reproductive

technology sorts of therapies, and I'd also like you to consider whether there is a difference on a need to consider the intentional use for infertility drugs, versus an inadvertent exposure to a pregnant woman of infertility drugs.

My last slide just reminds us of the rest of the morning's agenda. We'll be hearing from Drs. Kweder, Rodriguez and Bennett.

So if there aren't any questions from the Committee for me, I'll turn it over to Ricardo.

CHAIRMAN AZZIZ: I'd like to, before we continue with the morning session, quickly restate the question, so that all of us, both in the public and in the Committee, understand why we are here.

This morning's session has four questions, and I'm going to read them. The FDA can seek agreement from a sponsor to conduct certain post marketing, or Phase 4, studies to delineate additional information about a drug's risks, benefits, and optimal use. The Committee needs to provide advice on: a) when a Phase 4 pregnancy registry may be appropriate; b) when a Phase 4 agreement to conduct a pregnancy registry would be appropriate for drugs used in assisted technologies.

Two, if the FDA requires pregnancy registries for products used in ART, what types of information does the

Committee recommend bye collected at the time.

Three, what other mechanisms exist to collect this type of data or other information; and, b) does the Committee have any recommendations on how these or other mechanisms might be encouraged?

Fourthly, are there any other comments or suggestions for FDA on the two draft guidance documents which will be discussed this morning, which are: the "Reviewer Guidance--Evaluation of Pregnancy Outcome Data" and "Guidance for Industry--Establishing Pregnancy Registries.

Now, I'll restate these later in the morning when we begin the Committee discussion, but I do want committee members and public to keep these four questions in mind. This is what we are trying t focus on this morning.

Without further ado, I'd like to introduce Dr. Kweder.

DR. KWEDER: Do I have control over the slides, or do you want to--you. Okay.

Good morning, everyone.

As I introduced myself before, I'm Sandra Kweder. My day job is actually that I'm the Office Director for Office of Drug Evaluation IV. We oversee the regulation of all drugs to treat infection; so, antivirals, antibiotics, etcetera. But, in addition, one of my other

responsibilities is that one of the co-chairs of the FDA Pregnancy Labeling Task Force. And I'm here to sort of give you a broad perspective this morning on the work of that group, and activities within the agency relevant to pregnancy labeling. Many of the things that you'll be discussing later today are pieces of that.

So first, I'm going to give you an overview of the Task Force. Secondly, I will share with you some general direction and give you a framework of where we're going with the pregnancy section of the new drug label. And third, I'll give you a flavor for some of the other activities that we have ongoing.

I want to emphasize that the things that I'm going to be talking about are really things to be very broadly applied. We recognize, and have done studies--in fact, Dr. Weiss, who's at the table, was one of the initial investigators in some work that we did several years ago, looking at frequency of drug prescriptions for pregnant women; specifically excluding drugs that might be administered to treat obstetric--specifically obstetric-related indications. And, in general, I think it's safe to say that most pregnant women have at least one prescription during their pregnancy. That doesn't include over-the-counter drugs, and many, many women receive many prescription drugs during pregnancy. And we recognize that

we have not--we may not have served that population of patients or their physicians who are trying to prescribe them very well over the years. So the activities that we have ongoing are rather broadly related to that general set of circumstances.

Next slide. I want to just start with a few words about what I call "Labeling 101," and remind you that with the exception of drugs to treat conditions related to labor and delivery, drugs, for the most part, don't have indications for use in pregnancy. Products are approved more generally, if you look at the several thousand other products that are out on the market, to treat the conditions listed under "indications." We don't specifically say, "and in addition, this product to treat migraine headache is indicated for pregnant women with migraines." We--I mean, I can't think of a product that we have that would have that kind of wording.

Rather, the pregnancy section of the label is more akin to something that you might see related to additional descriptive information relevant to use in geriatrics, or pediatrics--although the pediatric picture is changing a little bit.

The section of most product labels that you're all familiar with is the pregnancy use section that first came into being in our regulations as something that we were

required to work with sponsors to include in labeling in the id 1970s. It was specifically designed to assist physicians--and I emphasize "physicians"--at that time patients didn't read labels. But it was designed to assist physicians who were actively prescribing for a pregnant patient. So they have a pregnant patient before them and they were deciding whether or what product to prescribe in pregnancy. It was never intended or anticipated that--by the folks who wrote this section of the regulations--that people would be in the position to think about what to do when a woman who was pregnant had already been exposed during that pregnancy to a product--during a time, for instance, when she didn't know she was pregnant. So I'll call that "inadvertent exposure issues," or "retroactive risk considerations." It wasn't designed to do that. Instead, it was supposed to provide simplified risk-benefit information for the prescriber.

You all know the pregnancy categories. I have "A" up here that, in the language that describes pregnancy category A is that controlled studies have been done in pregnancy and show that the drug is safe. I have a "less than one percent" there; that means that less than one percent of the products in the PDR have a category A designation.

Lonnie, you can just flip through them.

The rest are variations on how much animal data there is or is not, and how much human data there is or is not. And an interplay that sort of weaves in and out of there--of benefit.

The most commonly utilized category is category C--no surprise to anyone here, I'm sure. And category C, the requirements for that are that human data are lacking, and animal studies are either positive--they show something--or they have not been done. For many older drugs, the "not been done" applies, although that's unlikely to be the case in the future, because we now require them.

Next.

I want to give you a flavor of what our experience at the Agency has been over the years in applying these categories. And I'll separate that out from additional feedback from the public on them. But our experience has been mostly that in many respects these are frustrating, because most products have only animal data. And the nature of the animal studies--and this is not to be critical--but the nature of the studies is that they are screening studies. They are specifically designed in order to elicit findings--I mean, that's why they're done, and they're done that way intentionally. So positive findings are common; hence, category C.

And the science of this, in terms of how to take

those data and understand their positive or negative predictive value has not been worked out. So we can't say with a great deal of certainty that, for example, a positive in a specific organ system in a rodent model would likely translate into a similar positive, or something connected to it, in humans.

With regard to the categories themselves, there are no requirements in the regulations to update them, or to include additional information. It's really at the sponsor's discretion, and we've actually--the Agency has never been very vocal about that over the years.

Further, from the industry's perspective, it's quite clear that they often see it as in their best interest to include the most--the most--I don't know "scary" is not the word--but language that really warns to a degree that many clinicians find quite confining, and boxes them into the corner; when, in fact, that may not be warranted at all.

Further, it's difficult to change the categories. We have sponsors request to change categories from time to time, although it's not a common occurrence, and the biggest frustration is that the way the language of the regulations is written, you almost can never get rid of that category C, because the animal findings never go away. And that's very frustrating to work with.

And, finally, we've had extensive feedback from

users that I'll go into in a moment. I think, though, overall, the biggest challenge in this area that we continue to have to grapple with, and where we'd like to see some momentum for change is that this is an area of medicine--I think we can all agree--where the greatest certainty about risk is desired, but where we have the least data. And this feeds directly into some activities that we have, at the Agency overall has a huge initiative ongoing, led by the Commissioner, and our Center Director--out Center Director is Janet Woodcock--to do a better job and re-think our framework, and out involvement at the Agency, in risk management--and risk management including risk assessment and risk communication. And I think that pregnancy labeling offers a unique opportunity for us to do that better.

The Pregnancy Labeling Task Force is a multidisciplinary group made up of representatives from all centers in the agency, not just the Center for Drugs. They were established in 1996, with three major tasks that are pertinent still today. The first was to examine the current regulations. The second was to recommend changes for those. And the third was to consider the broader picture of related needs--and I'll explain what those are now.

To begin with, our examination of the current regulations, we held what's called a "Part 15 Hearing." Basically, a Part 15 hearing is a public hearing, without an

expert panel at the front; the FDA sits at the table and takes feedback from the public--broadly--on something that it wants to hear their views on.

In September of '97 we did that about pregnancy labeling, and we asked the following questions: Are the current regulations and their application to drug products relied upon--the categories, as we know them--are these things relied upon by practicing physicians? Are they useful? If so, how is it that they are useful? What is good about the system? What's bad about it? And if it's not informative overall, what suggestions do you have for change?

I have to say we didn't get very many suggestions for change, we had to tease those out--and I'll tell you about that in a minute.

Go ahead, Lonnie.

I can sum up in one slide--easily--the positive feedback that we got at that public hearing on the pregnancy labeling categories. In general, it was interesting to us to learn that the clinicians and the groups that we had feedback from overwhelmingly said that the categories are relied on by practitioners. That was a surprise.

The types of folks who have testified at the hearing included professional societies from a broad range of clinical medicine: psychiatry, dermatology, internal

medicine, pediatrics, family practice, and obstetrics. We also heard from patient groups and nurse practitioner groups.

What they liked about the categories is that they are simple; and that's very attractive. You can condense a lot--they liked the idea that it might be possible to condense a great deal of complex information down to single, ordered, letter categories. They liked--they thought that was good. It fits nicely in pocket handbooks in your lab coat.

But probably, most importantly, was that they thought, well, even if it has--if they have bad aspects, they're familiar and they're--they seem--all drugs have one--at least if they've--anything that's been improved since the late '70s, they have one, and we're at least familiar with it; it's something we know. People like--people don't like change.

Next.

I think I have, in one slide, the sample criticisms. I've honed this down from ten [laughs], just to try and condense this.

Despite the simplistic nature that was attractive about the categories, the number one criticism of the categories was that they are deceptive, and are overly simplistic. The lettered category system: A, B, C, D, X

appears to be risk-graded; the letters reflecting a degree of risk when, in fact, that is not the case.

Second, in their application over the years, very often unlike risks are grouped together within a single category, which creates--can create a great deal of confusion.

And, most importantly, there was a great concern that the simplistic category system, like letters in grade schools, foster a very passive approach to the interpretation of very complex information--and that we could do better.

And, finally, that even - the data within them, and the way that we've applied them over the years in describing what underlies a particular given category--that we have not done a very good job in describing that, even to folks who spend a lot of time thinking about animal data, and human data, and what its relevance is to the pregnant patient. It's often uninterpretable.

Next.

So our take-home message is--for a day's worth of testimony--were that the current system is actually quite uninformative, and it's so uninformative in its current use that it probably needs to be replaced and not revised.

Second is that risk communication--this was quite evident from hearing folks talk--has increased in

sophistication and in public attention over the 2 years since the regulations governing this section of the label were promulgated, and we need to bring up to date in that area.

So we did that by trying to take the pros and cons from that day and put them into a model that capitalized on all the things that people liked and didn't like. We decided to--this was--I have to say this is a really difficult task.

What we decided to do was try to at least find areas internally that we could agree on. There weren't a lot--I will tell you, this is--if it looks hard from the outside, it's even harder on the inside. We decided to take a concept paper approach and draft a concept paper that began to outline general sections of what a new pregnancy labeling portion of a label might look like. And in order to get feedback on that, we established a Pregnancy Labeling SubCommittee, that's actually a subcommittee of this committee, to meet in a public forum just like this--they met in June--and give us feedback on that label. And I'll tell you more about that shortly.

Go ahead.

In order to do this--to develop this concept sheet approach--I want to just give you just a few points bout FDA's philosophy about labeling in general--whether it's

pregnancy labeling, pediatrics, or general labeling.

First is that whenever we approach labeling we have a lot of data, as you can imagine, that needs to be consolidated into a very small space. Our goal, in working with sponsors or companies to develop these labels, that should be maximally informative to the reader, who would have a reason in the first place to be looking at this label. That doesn't always mean that they are exhaustively comprehensive. We can't possibly include everything there is to know about a product in a label. I mean, it just won't fit onto the page space that we have.

In general, we try to avoid speculation in the absence of data. We feel that, for the most part, there are other groups that are probably better equipped to do that; professional societies or other professional bodies that might put forward guidelines. We try to avoid doing that.

Now, if you sort of take those concepts, in general, and then think about how they might apply to the pregnancy sub-section of the label,e things get even more complicated. First, we have a paucity of data--as I've already alluded to. And because of the paucity--in particular, a paucity of human data, we have a very heavy reliance on pre-clinical or animal data that help us with this section. And, adding to that, is that we are well aware that increasingly we have a very diverse audience

who's reading these labels. We continue to--you know, first and foremost, keep with the tradition that these labels are developed for the prescriber; they're for medical professionals. But we have to constantly be aware that, particularly with the Internet and increased patient sophistication, understandably they are being relied upon by patient's as well. So we have to always have that in the back of our mind.

So our process in putting together our concept sheet was to pull together a multidisciplinary group within the Agency; mostly people from the Center for Drugs and the Center for Biologics. And our goal was to develop a structure and organization for the subsection of pregnancy labeling that would be sufficiently adaptable to wide variations in the amount of data one might have, and incorporate--and be able to be incorporated across the broad range of product categories--anything from vaccines, to biologic therapeutics, to drugs to treat pain, drugs to treat hypertension--anything. It has to be able to be adaptable.

And our general principles were that we felt, after hearing the public hearing testimony, that it's very important to distinguish anything that might be construed as advice or directives from risk information; and, again, to provide different levels of information that might be

relevant to different needs--in particular, even within the group of professionals. Some clinicians just want to know a bottom line. Some really want a lot of data, because they're--they like to sort of see data. Others don't want that.

Go ahead.

And so in a very simple form, what I have here to show you, is the three pieces of what might go into a pregnancy subsection of a label--and I'll walk through them in a little bit more detail. I'm going to--but I can't be exhaustive. We don't have time.

Each pregnancy--instead of a letter category, what one would see is a summary risk assessment, based on data that were available--combined animal and human data; a section that then addresses relevant clinical considerations; and then, finally, a subsection that includes a summary description of data that underlies, in particular, the summary risk assessment.

That summary risk assessment, which would appear first, would provide a concise overview of risk information., trying to get at a qualitative and quantitative risk assessment to humans where possible. We recognize that it's very important that we distinguish any risk assessment that's solely on the basis of animal data, and be very, very clear about that--as opposed to what might

be available from any human data.

The challenges of doing this--developing a summary risk assessment--are listed on the slide, and most important, they are how to provide the needed context, such as the relevance of animal data and applicability of animal data--and I've already--we've already established that the science of that isn't perfectly worked out--as well as in the case where there are human data, how those need to be put into the context of background risks that might exist, particularly in the area of birth defects--as a good example. And then of course, the challenge in and of itself, is how to come up with a system or language that communicates accurately any qualitative or quantitative aspects of risk.

And I would say--I think I'll refer to it again later--I think the biggest--one of the biggest challenges we have here is the risk communication, and the language of risk communication.

Go ahead.

In the clinical considerations section, the goal would be to provide the most specific clinically relevant information possible. That might be information that's relevant to unique morbidities of a condition in the pregnant patient. An example that I think is an extreme example, but is a good one to illustrate the point, is for a

drug that might be used to treat something like malaria. It would be important to communicate to someone who might not know this, that the morbidity and mortality of malaria in a non-immune person who's pregnant is extremely high for both mother and fetus. Okay? And that's an extreme example. You get away from the extremes, it gets a little more challenging.

And so doing this is tough. There are very few easy cases like malaria--God forbid malaria should be an easy case. But we need to think about how we might have to consider things like therapeutic alternatives in a given label; how to address inadvertent exposures, and how summary risk information might be differently interpreted in the clinical setting of inadvertent exposure versus active prescribing. And the final issue is how much advice FDA ought to be giving, and how specific that ought to be regarding monitoring during pregnancy. And I'll come back to this point.

And the "Discussion of Data" section, I think, speaks for itself. This would be a comprehensive presentation of available human and animal data; but, of course, how comprehensive does one need to be?--although I think this is something that we can work out.

Next slide.

We took this model to the Pregnancy Labeling

Advisory Committee in June. Dr. Greene, who's at the table here, is the chair of that subcommittee. And you can see on the slide that there are several members of this committee who also sit on that subcommittee: Dr. Dattel, Dr. Hammond, Dr. Janet Cragan, who's at the table, is a member of this subcommittee. We tried to include people who think a lot about some of these issues, from a variety of perspectives; clinical--and some of the other physicians you see here are, in addition to representing the field of obstetrics, represent internal medicine in an obstetric woman who represents internal medicine in an obstetric hospital; someone who cares for pregnant patients who, as part of primary care in an inner city section. We have several pediatricians, whose names you might recognize; folks from the teratology and genetic counseling community--and you probably recognize some of those names, as well. We had several consumer and patient representatives, epidemiologists, and people who think a lot about animal data--pre-clinical folks.

An interesting twist to this advisory committee that we have not done before, but will likely do increasingly, is we had two people on the committee who represent the pharmaceutical industry, which we think is an important group--an important group to represent as we evolve in this discussion.

Next.

I would say that the summary of their feedback, which was absolutely wonderful, could go on this slide. First, I think in general they thought that the model we had proposed is a good start. They had some very good suggestions for formatting that we're working with now. And I think one of the most important messages that we heard from the committee is that in this area of medicine in particular, the Agency needs to be very, very careful, and give advice quite sparingly, and be selective about when we're going to do that. You know, I think of it--you only have so many chips in your cup. You have to use them carefully.

And there was some discussion about whether or not there may be a role for a standardized panel of terminology to communicate risk. And we are working with that suggestion that we at least explore that currently. What it would look like remains uncertain. We didn't have any specific advice. And that's difficult.

Next.

So, n summary, I think for labeling the goals of labeling for us are clear. Our goal is to be--our most important goal is to be optimally informative in an area where there is often a paucity of data. Secondly, we need a system or a model that's relatively reproducible from one

product to the next, but has--and gives some structure for that, but allows us adequate flexibility to apply it as we need to for a broad range of products.

How best to implement this is a lot more complicated, and we are working on it.

I want to use this opportunity to tell you that we also have a large budget for focus testing, where we can--as we evolve a model we can take it out to groups of professionals, or patients, or whoever we want to test it on and seek their subjective feedback.

Go ahead, Lonnie.

Now, I'm going to move on and talk a little bit about the third goal of the task force--or the third charge to the Pregnancy Labeling Task Force--which was to consider the broader needs of pregnancy labeling. And what I have on the slide is pieces of a puzzle, because I think that the labeling itself is only one piece of the puzzle. It is not enough for the Agency to just say, "Well, we're going to change the way that we talk about drugs and pregnancy in product labels." Because our real problem is that we don't have data. And we would like to establish a process that drives data collection in a more meaningful way.

We also need to communicate the information that we have better than we've been doing, and that includes more and better dialogue with physician and consumer groups, and

in order to do that all effectively, we need to be able to have confidence that we have expertise available to us internally, and through our system of--through advisors and consultants with advisory committees, to get us that information and get us the advice that we need.

Now, in that area we have begun the process by establishing the committee I've already told you about to take big issues to. And secondly, we are beginning to try and enhance the knowledge of our own reviewers in the area of reproductive assessments, toxicology, and assessing--even beginning to think about--how to deal with case reports that we get all the time of adverse outcomes in pregnancy.

One of the documents that you have before you--and I'm not going to talk about this document any more than what I'm going to say here--is the clinical reviewer's guidance document on human pregnancy outcomes. That process of writing that document was started several years ago, because of the situation that our physicians in the agency face every day. And here's an example. The review division will have a drug to treat--let's say--urinary tract infections. It could be migraine headaches. It could be anything--that was approved several years ago. And across their desk comes a MedWatch report of an adverse outcome in a woman who may have been exposed to the drug in pregnancy. And it's a horrible case. You know, some child who was exposed in the

second trimester, and developed--you know, was born with a horrible neurologic deficit. And someone goes back and looks and sees that, "Ooh, mother took this drug X during pregnancy. Maybe it's related. I better report it." And the physician--I'll remind you, this is an infectious disease physician. And like most of our physicians--like most physicians in practice anywhere--they had an embryology course in medical school, and maybe they learned a little bit about prescribing in pregnancy when they did their OB rotation in third year of medical school, and maybe over the course of their residency and fellowship they saw 10 pregnant patients. And when the label got written for that product there wasn't any human data, so it was the animal toxicologist who gave it a pregnancy category C. And now they have this case report.

What do they do with that? Where does one even begin to think about how to assess a case, or think about data, or data sources? This guidance document was designed to help that reviewer begin to think about the problem, because there's no one place to go for that information, even if you look at text books, or go to the medical literature.

The second area of expertise that we're working with is in the pre-clinical area, for the pre-clinical toxicologists who do review all of our animal data. And all

drugs in development are required to have animal data related of their safety in pregnancy, and in relationship to any--and any--try to assess their risks to fertility, as well. Our pre-clinical people have been working on a reviewer's guidance document that tries to summarize an integrated approach to looking at those data. You don't have a copy of that document. It is available on our Web site. And we're not here to talk about it today. They've actually been doing a really good job of seeking expertise--outside expert advice from their own community on that document, as well. And I do believe that at some point it may come before our subcommittee to sort of get the human perspective on it, in addition.

Next.

So that's only the beginning of FDA expertise. In addition, we--some of our activities, in addition to the labeling itself, are targeted to the goal of trying to improve the human datas that we do get. And we have a new safety reporting rule that specifically says, "We are interested, in addition to many other things--drug companies who report to us periodically on their drugs--in you telling us in great detail what information you have that's relevant to the safe use of your product in pregnant women. Tell us about all your case reports. Get some professionals to help you interpret those. Don't just send us the cases. Really

do a better job than has been done before."

The industry--the guidance to industry on pregnancy registries--the draft that you have before you that was part of your background packet--is a piece aimed at doing this. Again, keep in mind that we need something that applies to all drugs, not just those used to treat conditions relevant to pregnancy and fertility.

I'll tell you that the genesis of the registry guidance document was the industry. We have a lot of folks who come to us and they say, "You know, we do think that our product is going to be used by a lot of women of reproductive age. And we know that some of these women are going to get pregnant. And we'd like to capture those data, so that we can decide what--better what the risk is in humans. How can we do that? We've thought about a pregnancy registry. We know that this company or that has done them before, but we can't really approach them about how to do it. Help us."

There's nothing in the medical literature that describes this. We've looked--because we tried not to have to write a document [laughs]. There's no one source for folks to go to. And some of the pregnancy registries that we see are actually that a company may keep a separate drawer in their file cabinet, where they keep their spontaneous reports of adverse outcomes in pregnancy

separate from their others. And that's their pregnancy registry.

We'd like to get away from that and begin to foster more meaningful discussion about data collection, standards for data collection, protocols, who the contacts should be, and things of that sort. And that was the genesis for the Pregnancy Registry Draft Guidance.

We have other activities that we're involved in. I think one of the things that would behoove us is to think more--to think out of the box about pregnancy registries. Maybe there are some different ways to do this. Maybe in addition to what companies do, we need to think about a centralized pregnancy registry that small companies, who can't--don't have the funding or the resources to run their own registry--could collaborate in a public-private partnership model.

We have a workshop that we're working on currently with the CDC And the NIH, to begin to discuss some of those issues. That workshop will be held in the spring of 2000.

We're working with the NICHD to try to begin to generate more interest in--by investigators in many fields in collecting pharmacokinetic and dosing data on women who are, because of medical conditions that they have, required to take drugs during a pregnancy in order to stay healthy.

And, finally, we recognize that one of the areas

that links this to a lot of initiatives that we have in pediatrics is lactation. And we have not done a good job at all in dealing with lactation and drug labels. And, in fact, in many cases we are--the position that seems to come across in the label, which is, "Mother, you must choose between taking this drug to treat your depression, and breastfeeding," is diametrically opposed to what the American Academy of Pediatrics is saying about the same product. And we need to work some of that out.

Next.

And other possibilities that we'll be addressing in the future, as I said, might be things--anything from new models for pregnancy registries and other study models, to using the FDA or other Web sites to provide more comprehensive information to practitioners who desire it; and to do more in the way of public outreach, with communication and education both for clinician groups and consumers in this area.

So, in summary, I think it's safe to say that there is a new model for pregnancy labeling coming. It's slower than we would like. However this is a very, very difficult problem and, in fact, someone whose advice I trust greatly, who has been around the Agency for a very long time, said to me, "I can't believe that we're actually doing this. This is--in my 30 years at the Agency, this is the

hardest thing that we have ever done."

As you can imagine--you know, we're dealing in an area with a paucity of data, but an area about which most of us, understandably, have very deep-seated feelings. And we need to tease out the feelings from the science, and try to do a better job to be more informative. And we're committed to doing that.

Thanks very much.

CHAIRMAN AZZIZ: Thank you very much.

I'd like to open the floor for questions to Dr. Kweder, particularly from the committee.

A couple of announcements. First, I'd like to have Dr. Hammond introduce herself. She wasn't here.

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

CHAIRMAN AZZIZ: Secondly, anybody who has beepers or cell phones, put your beeper on buzz, if you would. And if you have a call to make, please leave the room. It does disturb the rest of us. Thank you.

Questions for Dr. Kweder?

[No audible response.]

CHAIRMAN AZZIZ: Dr. Kweder, in your presentation--just for my--you had a--you presented a series of steps that are being undertaken at this time. You are

not asking the committee specifically to comment on those steps at this point.

DR. KWEDER: It wasn't my purpose, but if you'd like to, I'm certainly open to any comments. But that wasn't the purpose. It was to try and give a general perspective of where some of your work might fit in.

CHAIRMAN AZZIZ: If there are no questions, we'll continue.

Dr. Rodriguez, Director of the Division of Drug Risk Evaluation will present.

DR. RODRIGUEZ: Good morning.

Today I'll be presenting the FDA's industry guidance regarding the establishment of pregnancy registries. And I am the co-chair of the Pregnancy Registry Working Group, which is a working group under the Pregnancy Labeling Task Force. And Carolyn McCloskey did the lion's share of actually designing the draft of this guidance. Also, Sheila Weiss, Jean Manson, and Anthony Shiali were special government employees who helped us draft this guidance, as well.

Well, why did we draft this guidance? Industry has asked the FDA for specific advice and recommendations regarding this issue for Phase 4 recommendations, and to update the labeling of currently marketed drugs. Because of this need for advice and recommendations by industry, CDER

and CBER has drafted this guidance.

The purpose of this guidance is to serve as a resource document regarding the quality and integrity of data, and the adequate documentation of the research methods used. Registries should be designed for products with unknown or suspect adverse human pregnancy outcomes, not for known teratogens. The purpose of pregnancy registries is to determine the existence of major risks; to estimate the magnitude of those risks, whenever possible; to identify risk factors; and to identify any short-term pregnancy outcomes of interest. In addition, registries can also be used to identify any long-term post-natal outcomes of particular interest.

The problem--as Sandy said earlier--is the lack of human data. Some animal studies may indicate a possible human adverse effect, but translation of animal studies to the human experience is difficult. If an effect is seen in animals, does that mean a similar effect should be expected in humans? Conversely, if no effect is seen in animals, does that mean no adverse effects will be seen in humans? These are very difficult questions of answer.

For drugs already on the market, spontaneous case reports are difficult to assess, because these are reports that are made after the adverse outcome is known. Also, outcomes like birth defects are not rare. These occur in

about 3 to 4 percent of pregnancies.

Regarding randomized clinical trials, pregnant women are excluded from trials and dropped if they become pregnant during a trial. As a result, we usually have no meaningful pregnancy and fetal data available to us before a drug is marketed.

Exposure during pregnancy to a broad range of drugs can be extensive. Inadvertent exposure may occur during most of the first trimester, before a woman is aware that she's even pregnant. And for the treatment of chronic conditions, women don't have a choice. Exposure may continue, even with the recognition of pregnancy, for treatment of underlying medical conditions.

What are the current limitations for assessing risk? Spontaneous reporting systems can yield signals about adverse outcomes that are difficult to assess. Outcomes can be very common. For example, spontaneous abortions occur among 15 percent of pregnancies. Another reason they're difficult to interpret is because they're retrospective reports by definition; that is, they're reported after the outcome is already known, and they're biased toward abnormal outcomes. And a corollary to that is that there is underreporting of normal outcomes. So it's very difficult to make an assessment of risk.

Pregnancy studies, pregnancy registries or

observational studies of exposed and/or unexposed mothers--for example, mothers with diabetes, mothers treated for asthma, and so forth--there's voluntary registration when mother is exposed to a drug during and/or before a planned pregnancy, not after the outcome is already known. Registries may be designed to compare pregnancy outcomes of drug-exposed to unexposed mothers.

Critical baseline information should be collected at registration, such as maternal age, previous pregnancy outcomes, medical conditions, smoking, and other drug therapies, or any other variables of interest during pregnancy that may impact the adverse outcome of interest. The focus of the registry should be the collection of prospective cases; that is, cases that are enrolled during pregnancy before the outcomes are known. And although retrospective cases may be collected, these data should be analyzed separately.

When are pregnancy registries needed? That is, what specific categories of medical products should be considered? Any drug, particular new molecular entities with high use by women of childbearing potential should be considered; also, live attenuated vaccines or other products with sub-clinical infection in the mother; any product continued during pregnancy for the treatment of underlying maternal medical conditions; also products suspected of

adverse effects, due to their structure or pharmacologic activity, pharmaceutical class, or animal studies, or spontaneous human case reports--perhaps ascertained internationally before products have been marketed in the U.S.; and products known to be harmful, but risk not quantified during human pregnancy.

What should be the timing and scope of pregnancy registries? Well, we think the first five years of marketing may be the best time, to ensure early enrollment of exposed women, to glean any learning that we can glean from the necessary exposure of this drug--early on. It should include a diverse and broad population of women, and domestic and international reports should be considered, if at all feasible.

What are the design considerations in pregnancy registries? One should identify the expected prevalence, the pattern of use, and the cumulative dose of the product during pregnancy. One should also identify the expected patterns of product use by trimester or fetal exposure and, for example, whether the drug is to be used chronically or intermittently during pregnancy.

One should also identify and define outcomes of interest, and assess the background rates of adverse pregnancy and infant outcomes from the population under treatment. One should include plans to validate maternal

and/or health care provider reports with medical records, if at all feasible.

One should define the prospective study requirements for enrollment; that is, enrollment after exposure but prior to the outcome. One should define the eligibility criteria before collecting the information. And if retrospective cases will be collected, these should be analyzed separately in a case series format.

One should define all the case definitions, a priori, for all the outcomes of interest in pregnancy, labor and delivery, any specific birth defects of interest, and any other infant outcomes. One should identify the standard baseline information to be collected at enrollment. And one should consider validating outcomes with a second source.

Follow-up is critical in the design consideration. One should describe the standard procedures for follow-up to ensure that the money, the time and the effort spent to enroll women is wisely used. One should specify the criteria to define cases that are active, those that are pending, and those that are considered lost to follow-up. The reasons for close follow-up are obvious. They're to update the exposure and testing information throughout pregnancy, and to enhance recall of the patients and providers; and to identify any pregnancy losses during pregnancy, which may be an outcome of interest, and which

may be very difficult to ascertain.

Consideration should be made in including and selecting comparison groups; for example, a comparison group may be women who were exposed to another product in the same class for the same medical condition. Alternatively, there may be multiple comparison groups that one can entertain. But if no comparison group is going to be employed, then a comparison to an appropriate estimate of the background rates of outcomes of interest will be critical.

Other design considerations are statistical considerations; considerations in sample size, and considerations in comparisons of background rates of adverse pregnancy outcomes, with the outcomes of interest. The data analysis plan should include how the data will be stratified or separated, and then outline the comparisons to be done between prospective and retrospective cases, if any. The plan should outline the calculations of risk by specific outcomes; whether by comparison groups and/or by the use of background rates.

The guidance document was published in early June, and was available for public comment for 90 days. The public comments regarding this guidance include sand endorsement by the Organization of Teratogen Information Services, as well as some industry concerns that largely fall under the following categories: clarification of

purpose--that is, the purpose for the FDA to draft a guidance for industry, and the purpose that industry may have for establishing registries; methodologic questions regarding the design of registries; cost issues--in particular, those incurred when one needs to assess long-term outcomes of interest; clarification of reporting requirements--right now, birth defects are considered spontaneous reports that are subject to 15-day reporting requirements, so there's a plea for reconsideration of that for the future; and also, that FDA should provide a review of any existing drug registries that we can learn from.

I can entertain some questions now, if there's interest to do that.

CHAIRMAN AZZIZ: Thank you--yes. Questions from the panel?

[No audible response.]

CHAIRMAN AZZIZ: I have a question regarding the concerns of industry. I think those questions are all very valid. We'll try to address these in the discussion later on.

Is this something that the Division is actively addressing at this point--the--

DR. RODRIGUEZ: Which division?

CHAIRMAN AZZIZ: The industry concerns--clarification of purpose, methodologic questions

and so on.

DR. RODRIGUEZ: This is something that our group, with Sandy Kweder, is entertaining. Our specific working group is tasked to take a look at these comments and incorporate or respond to these comments.

Sandy, did you want to add anything to that?

DR. KWEDER: Yes--the--its actually interesting--the process that we have for any draft guidance document is that we will take any and all public comments, and we'll sort of take them back, read the draft and make changes as we see appropriate, taking into consideration all of the concerns and comments that are raised.

In general, whenever we put out guidance documents, because they affect the industry most directly, we always--it's the norm that those would be the comments that we consider the most significantly. Sometimes it's a matter of--that there are things that require clarification. One of the things that Evelyn mentioned there as one of the concerns was simply an error that we need to fix. And so we do take those into consideration.

Whether or not we change our position on an issue because of the comments--sometimes. But usually it's maybe a modification or, you know, sort of moving more towards the middle.

CHAIRMAN AZZIZ: Thank you.

Any questions from the committee? Dr. Trussell?

DR. TRUSSELL: The intention appears to be for new products that will come onto the market--you focused on the first five years; gathering information in the first five years.

Is the intention also ever to move to pregnancy registries for the thousands of products that you now have but have no data on?

DR. RODRIGUEZ: I think if industry is interested in starting a registry they may, of course, indeed do that. This is, of course, a guidance--a suggestion for industry to take into consideration. If there's a need--a perceived need by industry to change their labeling, they may want to undertake a registry in order to assess their question.

DR. KWEDER: I can add to that.

One of the--if you think about how the FDA works, which is , you know, in terms of working with industry on any specific initiative, we have the most opportunity to have an impact when a product is new. That's when we have the most leverage, such as to make something a face for agreement with an industry.

When you get older products on the market--and, certainly, in the area of assessing risk in pregnancy, many older products are of concern to most of us. We don't have very much opportunity or leverage to do that, particularly

when you have something that's been generic for a number of years, and there are a number of manufacturers who actually produce the product. That's why this guidance document helps us deal with products that are newer, but we recognize that we have to think beyond that, and think about other ways of collecting information on products that are older, or--particularly those that are older and also generic; and think about other methods of data collection that we can work with the industry in some sort of partnership arrangement to collect data on.

CHAIRMAN AZZIZ: Just as a point of clarification: these are guidelines, again, for industry, primarily, and reviewers. This is not an enforcement of the need for registries or anything like that. That is a separate area. Right now it's simply guidelines.

Dr. Rodriguez, thank you very much.

DR. RODRIGUEZ: Thank you.

CHAIRMAN AZZIZ: We're going to take a 15 minute break. It is 10:15. We'll meet at 10:30 and continue.

Thank you.

[Recess.]

CHAIRMAN AZZIZ: If we can remain on time, please.

The net person I'd like to introduce is Dr. Ridgely Bennett, who will be speaking to us on the Impact of the draft Pregnancy Guidance on Products Reviewed at the

DRUDP, particularly ART drugs.

DR. BENNETT: Is it on now?

Good morning. I'll try again.

The guidance for industry for establishing pregnancy registries focuses on establishing registries to assess suspected or unknown risk to pregnancy outcomes from exposures to specific drug products. Most of our concern would be the unknown risk of new drugs. At the time of a product's marketing, there are seldom meaningful human data on the effects of that product on the fetus. Depending on the indication and characteristics of the patient population, women may be exposed inadvertently to a given product prior to recognition of their pregnancy, or they may be exposed to the product during a recognized pregnancy. It is virtually impossible to prove that a drug is not teratogenic. Conversely, it is very difficult to prove that a drug is teratogenic, unless it is relatively potent.

The guidance has a special impact on some of the drugs reviewed in our division. Our focus today is on drugs used in assisted reproductive technologies--called "ART" or ART. It is not uncommon for four different drugs to be used in one ART treatment cycle. With the exception of progesterone, these drugs are administered before the patient is pregnant, and not during pregnancy. If there is a detectable risk to the resulting fetus, how does one

determine if it is drug-related and, if so, which of the four drugs is responsible? Is it more efficient to search for detectable risk to the fetus resulting from the ART procedure itself, rather than from a specific drug? After all, ART procedures include the use of devices, culture media, etcetera, as well as drugs, any of which could be the cause of teratogenic effect. A detectable risk to the fetus could be due to something other than one or more of the drugs administered.

There are several ART procedures used today. I will simply mention them, and tell you what they have in common. They involve aspects, other than drugs, including laboratory procedures, that could be responsible for congenital malformations.

Assisted reproductive technologies can be defined as end-fertility procedures that have in common the manipulation of oocytes, spermatozoa and/or embryos. Some commonly accepted procedures included under ART are controlled ovarian hyperstimulation and intrauterine insemination. This involves ovulation induction combined with timed separation of spermatozoa from seminal fluid, with suspension and buffer, or culture media, and insemination into the uterus artificially with a syringe.

In vitro fertilization and embryo transfer--or IVFET--this involves laboratory culture of aspirated oocytes

and spermatozoa, combined in a laboratory dish, followed by trans-cervical embryo transfer using a catheter if fertilization occurs.

Intra-cytoplasmic sperm injection--or ICSI, or "iksee," this involves a single sperm being injected into an egg's cytoplasm.

Gamete intrafallopian transfer--or GIFT--is the direct placements of aspirated oocytes and washed spermatozoa into fallopian tubes, using a catheter during a laparoscopic procedure.

Zygote intrafallopian transfer--or ZIFT--is the laboratory culture of aspirated oocytes with spermatozoa, followed by direct placement of fertilized zygotes into fallopian tubes before they start to divide.

Tubal embryo transfer is the laboratory culture of aspirated oocytes with spermatozoa, followed by direct placement of embryos into fallopian tubes.

Frozen embryo transfer is the uterine or tubal transfer of thawed pro-nuclear stage zygotes or embryos.

Oocyte donation is the laboratory culture of aspirated oocytes from a donor woman, followed by IVF or GIFT.

Host uterus--also known as a gestational surrogate mother--this involves embryos generated from the intended parenting couple, and the transfer of these embryos to a

normal fertile woman for the purpose of carrying a child and relinquishing it to that couple.

Newer experimental ART techniques include cytoplasm transfer, genetic pre-implantation analysis, implantation of frozen ovarian sections, ovarian nuclear transfer, laser-assisted hatching, and blastocyst transfer.

All of these manipulative procedures involve aspects, other than drugs, that could possibly be the cause of any increased incidence of major congenital malformations. Within the Food and Drug Administration, three centers are involved independently in the regulation of assisted reproductive technologies. Our center, the Center for Drug Evaluation and Research, is involved only in the regulation and approval process of new drugs that are used in the ART treatment regiment. The Center for Devices and Radiological Health regulates numerous devices, such as catheters, syringes, pipettes, etcetera, that are used in ART. The Center for Biologics evaluation and research regulates, or proposes to regulate, human cellular and tissue-based products, including reproductive cells and tissues. Other agencies within the Department of Health and Human Services are also involved in various activities related to ART.

The Office for Women's Health has convened and interagency working group to discuss and share information

on each agency's activities related to ART. The Secretary of Health and Human Services recently appointed a Genetic Testing Advisory Committee to advise the Department. This action could have relevance for ART techniques, such as genetic pre-implantation analysis.

The Centers for Disease Control and Prevention, the National Institutes of Health, and the Health Care Financing Administration are also involved in various related to ART.

Our focus today is on the kinds of drugs commonly employed in ART treatment cycles, and the need for pregnancy registries of babies born resulting from such treatment. These drugs include GnRH agonists and antagonists, human menopausal gonadatropins, purified urofollitropin, recombinant follicle stimulating hormone, chorionic gonadotropin, and progesterone. It is not unusual--as I said before--for four different drugs to be utilized in one treatment cycle.

Following the thalidomide tragedy, birth defects monitoring programs proliferated in many parts of the world, including the United States. In 1967, the Centers for Disease Control started a surveillance system in metropolitan Atlanta, and in 1974 initiated the first nationwide monitoring system. In 1974, the International Clearinghouse for Birth Defects Monitoring was created, and

in 1979, the EuroCAC project was started--that's the European Community's Concerted Action on Congenital Anomalies.

Between 1981 and 1985, 11 states passed laws to establish birth defects monitoring programs in the United States. Several registries and surveys, specific to IVF babies have been established around the world. A collaborative survey in Scandinavia--IVF in the Nordic countries, 1981 to 1987--was established. The British Medical Research Council Registry was established in 1983. The U.S. National IVFET Registry was established in 1986 as a collaborative effort between the Society for Assisted Reproductive Technology--known as SART--of the American Fertility Society and Medical Research International. The objectives of the registry are to document rates of pregnancy and selected birth outcomes; identify optimal treatment profiles for different patient groups; and act as a follow-up program capable of detecting and measuring possible short and long-term adverse health effects on women and their offspring.

The report for the year 1995, published in March of 1998, was the first report in which ART outcome reporting was compiled and cycle-specific data submitted to a central depository in cooperation in cooperation with the Centers for Disease Control and Prevention. In the 1996 report

published in May of this year, there were 14,054 normal IVF babies. Structural or functional defects occurred in 1.8 percent of total neonates--well within the range of major malformations occurring within the general population.

The 1997 results are expected to be published later this year. We have relied heavily on this national registry through the years for information regarding any congenital malformations that occurred in ART babies at birth in the United States, however there is no follow-up reported of babies past birth. The French IVF national registry was established in 1986, and is managed by the French National Institute for Health and Medical Research. The Fertility Society of Australia, National Perinatal Statistics Unit, established its registry in 1989. The United Kingdom Human Fertilization and Embryology Authority was set up by an Act of Parliament in 1991 to oversee the working of the Act, which deals with many aspects of assisted reproduction including a registry of pregnancy outcomes.

The world report after IVF, GIFT and ZIFT was published in 1992. The Israeli Association of Fertility also maintains a national registry of IVF births. None of these registries or surveys have detected an increased incidence of major malformations in IVF-without-ICSI babies at any time above that found in the general population. In

addition, congenital malformations in babies born to mothers who became pregnant during clinical trials as a result of treatment that included these drugs have never exceeded that found in the general population.

Examples of the type of pregnancy outcome data available a the time of approval of a new drug used in ART are shown on this slide. The initial safety database for the GnRH antagonists contain 73 neonates. The final safety database contained a total of 283 neonates born during the clinical trials. Typically, the labeling for these products will give you this information for the drug, along with mentioning of the specific malformations, and a statement that the causal relationship between the malformations and the drug is unknown. Although frequencies of congenital malformations as a whole have not exceeded that of the general population, the numbers of neonates are often so small that significant risk for various specific malformations are not excluded. Also, spontaneous reports of congenital malformations in FDA's Spontaneous Adverse Events Reporting System associated with drugs used in ART give no indication of an increased incidence of major congenital malformations.

Considering our present state of knowledge, what, if anything, is a reasonable next step to take to ensure we detect any unknown risk of new drugs used in ART procedures?

Should pregnancy registries for each new drug approved be established? For such a registry to work, there would need to be provisions for patient enrollment, follow-up, updating of entries, analysis of data, and establishment of reference groups for comparison. Differences in ART procedures would have to be taken into account, along with other confounding factors. Registries have typically not included this kind of detailed requirement.

How do we apply the principles of pregnancy registries to drugs used in ART? What level of risk is acceptable? How confident should we be about this level of risk? What are the pros and cons of relying on data from the U.S. SART registry prepared by the Society for Assisted Reproductive Technology, and the Centers for Disease Control and Prevention to determine if there are increased risks of congenital malformations in ART babies? Does it provide sufficient data to satisfy our needs?

Any suggestions you make that will help us to detect unknown risks that may occur in association with the drugs used in ART treatments will be appreciated.

Thank you.

CHAIRMAN AZZIZ: Thank you very much.

We're open for questions?

[No audible response.]

CHAIRMAN AZZIZ: Well, I have a question, to begin

with.

In your definition of ART, you mentioned the manipulation of oocytes, spermatozoa and embryos, and that, of course, leaves out the controlled ovarian hyperstimulation only. You obviously included IUI there to sort of fit it into your definition, although that seems to be very artificial, in the sense that you've included IUI, that makes it ART according to the definition. If you do it without IUI you're not. And I think perhaps you can address for us that, because it seems like a sort of a--I don't know, a loophole, or just sort of an area where you can have a drug, have it only for controlled ovarian hyperstimulation and, hence, perhaps not fall into any of this, which is actually sort of an arbitrary difference.

DR. BENNETT: Well, it wasn't intended to have any special meaning. As you well know, this is simply one of many definitions of ART. So you could really pick your own definition.

CHAIRMAN AZZIZ: But the reason I'm asking that is: as we come up with recommendations or comments regarding ART and pregnancy registry, I'm not sure--I mean, we're pertaining to the drugs which can be used for anything from controlled ovarian hyperstimulation alone--

DR. BENNETT: Yes.

CHAIRMAN AZZIZ: --to that. So I just want to

make sure that it doesn't exclude that.

DR. BENNETT: It does not.

CHAIRMAN AZZIZ: Okay.

DR. GREENE: I'd like to ask a couple of questions.

As you mentioned, it's difficult to separate, in some cases here, the drugs that are used as part of ART technology from the manipulations which occur in the antibiotic. And one of the questions--one of the concerns that has been addressed is whether there is an increased incidence of some problems as the result, possibly, of manipulation in the laboratory. And that's going to be very difficult to separate from the drugs.

DR. BENNETT: Yes.

DR. GREENE: Specifically, the definition of a congenital malformation I think needs to be broadened slightly to include monozygotic twinning as a congenital malformation. And, certainly, in the textbooks, monozygotic twinning is considered to be a congenital malformation, and there is at least some concern that, whether it's the drugs or the manipulations in the laboratory, may lead to an increased incidence of monozygotic twinning.

And I guess my first question is: has there been any concern or--about that?

DR. BENNETT: Well, there's always concern about

that. I mean, you know, there are many other factors which we haven't specifically mentioned that you are well aware of: multiple births, age of the patient, etcetera, which have a bearing on this.

DR. GREENE: If I could pursue this--another problem which is a direct result of this technology is the problem of prematurity, and the complications that result from prematurity--and often severe prematurity. And most importantly, and of greatest concern, is the problem down the road of cerebral palsy as the result of severe prematurity. That's a much more difficult end-point, of course, to assess, because the diagnosis of cerebral palsy is not usually made until at least two years of age or thereabouts.

Is there any provision to extend the surveillance to pick up that end-point?

DR. BENNETT: Well, I think that's something that the Committee will discuss this morning and give us some suggestions on how long this should actually go on. Should it be two years? Five years? 20 years? I think that's a valid point of consideration.

DR. GREENE: And, if I may--one other question, and that is that your presentation focuses upon the safety of these technologies for the fetuses and the infants produced. It doesn't mention, specifically, the women. And

what surveillance is required with respect to the risks and complications to the female patients that are undergoing these assisted reproductive technologies, both in the sort-term--the obvious, immediate consequences of ovarian hyperstimulation; the degree to which it can be controlled is sometimes difficult, really; and also, the question which has at least been raised as to whether the hyperstimulation may have adverse consequences in the long term on incidence of ovarian cancer.

DR. BENNETT: Well, we have no information on the ovarian cancer issue. As you know, that's been an ongoing issue for years, and if I would summarize my understanding of the information that is available as of today, there would seem to be not an association. However, I'm sure that there are many people who would disagree with that, and present their data to try and support their view.

As far as follow-up of women, generally in the clinical trials, most of these are single-cycle treatments. There may be two or three treatment cycles, and essentially, whatever is going to take place is going to take place during that treatment cycle, or soon thereafter. We don't usually have any sort of follow-up data on that particular patient, other than the outcome of pregnancy and months to follow that.

DR. GREENE: But issues such as ovarian

hyperstimulation syndrome--would that be recorded?

DR. BENNETT: Yes, it would be.

DR. GREENE: Okay.

DR. BENNETT: That's probably one of the most serious adverse effects that we are concerned with.

CHAIRMAN AZZIZ: Just a point of protocol--if you would just mention your name before making comments, that will help the transcriptionist. Thanks.

DR. FALK: Richard Falk, from Washington, D.C.

One of the most spectacular--for want of a better word--examples of a hormonal problem in pregnancy--hormonal teratogenicity in pregnancy was the diethyl stilvesterol episode, which took a whole generation to diagnose; not being diagnosed until the offspring became pubertal.

That's of great concern to me when we're talking about the effect of hormonal perturbations in pregnancy and follow-up. You mentioned that the SART data is limited and, in fact, all--or most of these follow-ups are limited to one year, two years, three years--whatever the long-term is. And, of course, I think, for practical purposes, they have to be monitored literally for a generation.

Yet, I can tell you as a practitioner of assisted reproductive technology that the economics of even filling out the SART data is very oppressive. Many--more and more programs are electing not to comply with the SART

regulations simply because of the overload of paperwork. If one had to follow thee recommendations to these logical conclusion, I fear it would just not be a practical solution. And I think one has to take this into serious consideration--and I don't mean give up on it, but I mean to figure out how this is going to be effected; how is it going to be funded, to have long-term follow-ups that are needed on these patients; how is it going to be practically handled?

DR. BENNETT: Well, I think the idea at the present time is that these pregnancy registries would be funded by the drug company.

CHAIRMAN AZZIZ: Just, again, a comment--we're going to be able to, in Committee, obviously discuss and provide a lot of the controversies. I'd like to see if we could just have specific questions for Dr. Bennett.

By the way, for the Committee members, if you just simply press your button while somebody else is speaking, you'll be in line to speak up. These new-fangled speaker phones are working that way.

Bonnie?

DR. DATTEL: I wanted to again ask the question about--Bonnie Dattel--sorry, from EVMS.

I wanted to ask the question about follow-up of women who have undergone these treatments. Now, I, of

course, do take care of theme when they do get pregnant, but I don't see the failures. And I think that, contrary to what you've stated about one or two cycles--that that is not always the case; that I have seen patients that have had between six and 15 cycles. And is there going to be any provision for following up treatment failures in these women, and what limitations on numbers of cycles? You know, we're beginning to get that data for beta methazone for fetuses, and so i'm concerned that treatment failures, and multiple cycles, and doctor shopping maybe an issue, and I wonder if we have any provisions for that?

DR. BENNETT: Well, at the present time, we only have the data from the clinical trials. There are no Phase 4 studies as such--which is the discussion of this meeting this morning, dealing with pregnancy registries. But for clinical trials there's usually--usually very limited data.

CHAIRMAN AZZIZ: Dr. Bennett, thank you very much.

We now open initiate our second open public hearing. We have one speaker, and there is certainly time, if somebody else needs to speak.

First speaker is Doris Haire of the American Foundation for Maternal and Child Health.

Ms. Haire.

MS. HAIRE: Good morning. I'm also representing the National Women's Health Alliance.

I understand that the purpose of the Pregnancy Registries is to provide FDA reviewers and sponsors with guidance on establishing registries on pregnancy outcomes from an exposure to specific medical products. Yet, in reading through the proposed "Guidance for Industry," I found nothing in the text that specifically addressed the category of drugs most commonly used in pregnancy--obstetric drugs used during labor, birth and lactation. At no other phase of pregnancy is the fetus more likely to be exposed to a plethora of powerful drugs which have never been scientifically evaluated and found to be safe for the fetus.

By the way, the FDA category of "A"--at least I was in on the very beginning of those discussions years ago--but it does not say that controlled studies in humans have been carried out, and that the drug has been shown to be safe for human fetuses.

The FDA and the scientific community have been very open about the potential for harm involving drugs administered during organogenesis. Why, then, is there a reluctance to remind the public that, as the time of birth approaches, it is the fetal central nervous system that is most vulnerable to drug-induced changes? Even the "General Consideration for Clinical Evaluation of Drugs in Infants and Children," written in 1974, acknowledges the potential of obstetric-related drugs to alter neuronal maturation,

cell migration, dendritic arborization, cell differentiation, and myelinization within the central nervous system of the exposed fetus and newborn.

Until the late Franz Rosa--Dr. Franz Rosa died, it was my custom in the past to check on a specific drug report which had been reported to me by a doctor or parent, and that it had been officially filed with the FDA. I regret to say that through the years, not a single such report was ever filed with the FDA. So we should not assume that the drug-related adverse effects on the fetus and newborn will be voluntarily reported to the FDA.

The FDA has taken no steps to prevent another disaster, such as that involving diethyl stilvesterol from occurring again. New YOrk State law requires every hospital obstetrics service in the state to provide every prospective maternity patient with a brochure which details the obstetrics service's rate of cesarean section, induced labor, augmented labor, forceps, vacuum extraction; but when the nurses and midwives see the data for their particular service, they often burst out laughing, because the data reported is often a far cry from what they observe in their daily service.

How can the public trust industry or the medical community to voluntarily report adverse drug reactions? I recently attended a meeting at the New York Academy of

Medicine. It was primarily attended by pediatricians and behavioral scientists. The focus of the meeting was neurologic dysfunction among children in the United States. By the end of the meeting it was clear that at least 15 percent of the children in the United States have some form of brain dysfunction.

Last week I attended a national conference of CHADD in Washington. CHADD is an organization dedicated to providing help and services to families with children with learning disabilities and attention deficit disorder. The ballroom of the Washington Hilton was filled with over two thousand teachers who are to go back to their communities and deal each day with learning disabled children; children who will have very little chance of ever reaching the educational potential--excuse me, the educational level and earning potential of their parents.

Drugs used in epidurals have been shown to adversely affect neurologic function in the neonate for at least four or six weeks after birth. And that doesn't mean that the effect stopped. It only meant that they stopped testing.

The FDA should not ignore the growing evidence that there is a potential link between intrauterine exposure to obstetric-related drugs, and brain dysfunction in the exposed offspring. Twenty years from now those of you who

are still here may wonder why it took so long to recognize these potential risks.

I urge the FDA to include and require pregnancy registries for all obstetric-related drugs--not just new drugs, but all obstetric-related drugs--in order to compile post marketing on the adverse effects of these drugs on the subsequent neurologic development of the exposed offspring.

I don't understand why a woman should be dropped out of a trial because she is pregnant. I only received the printed information on Friday, so I may be remiss by not understanding that. But I would like to have that clarified today.

I thank you for this opportunity to comment.

CHAIRMAN AZZIZ: Thank you.

Are there any other speakers that wish to make comments?

[No audible response.]

Seeing no further speakers, we will open the discussion from the Committee.

Let me--what I'd like to do is begin with the first question, restate it, and then have the Committee discuss it. We will try to limit our entire discussion to 15 minutes per question, but that does not have to--it's not written in stone. It just depends on what we produce.

The first question is: We need to provide advice

on when a Phase 4 pregnancy registry may be appropriate, and when a Phase 4 agreement to conduct a pregnancy registry would be appropriate for drugs used in ART.

Let's take that first one: when a Phase 4 pregnancy registry would be appropriate. Comments from the panel.

[No audible response.]

CHAIRMAN AZZIZ: This is a very quiet panel.

Dr. Greene.

DR. HAMMOND: Oh, okay--go ahead?

I think that any drug that would be designed to be used for people who are going to become pregnant it would be important. I think a drug like Cronone, which we have in our packet here, which was recently approved, and which is designed to be used for infertility, but also in women who are pregnant, you should have registry for. That would be number one.

And number two would be drugs that are commonly used by pregnant women.

DR. GREENE: I guess--Mike Greene.

I guess what I would like to hear is an argument why this shouldn't be part of every drug's introduction in the same way that the first three parts of drug testing are part of the introduction of every new product--except as outlined in the document, for products that are anticipated,

or reasonably expected to cause problems, where exposure should simply--straightforward be avoided, like Acutaine. But barring a drug where it clearly--exposures during pregnancy should clearly be avoided, why wouldn't this be part of every drug's introduction?

CHAIRMAN AZZIZ: I think that's part of what we need to discuss here. I mean, I have a similar concern. Remember that we are referring to the draft document that was drawn up, so I think that the more we can focus on modifying or commenting on that draft document may be helpful.

But--for example, on the page 5, there seems to be a contradiction in the document, in that it states that "pregnancy registries aren't likely to be requested in the following situations," and it goes on--1, 2 and then 3: "the product is not intended for use in women with reproductive potential." Yet, I think, very clearly, on page 7, the draft goes on to state that: "If the potential for off-label use exists, these numbers should also be carefully estimated."

I think that that is a contradiction in terms. I mean, I don't think that stating when the pregnancy registry is unlikely--and particularly including "the product is not intended for women with reproductive potential"--that allows, or provides a misleading guidance, in the sense that

most drugs, in fact, will be usable by women of reproductive potential, and there are very few drugs that will be absolutely not usable by women. So, although I understand why that statement is there, I think there is a contradiction and it may need clarification. And I think it touches on Dr. Greene's point that, actually, a large number of drugs may be a candidate for registries.

DR. KWEDER: I think--I just want to comment on that.

I think you're right, and perhaps some of that reflects the people who were writing this draft guidance document were almost--may have had an underlying expectation that drugs that were intended for use in a population of patients who would be likely to become pregnant would be studied--something--in registries--well, naturally, or in addition to other methods of longer-term follow-up.

But your point's very well taken.

DR. HARRIS: Yes--Joseph Harris.

I think part of the problem here is that, really, the ethical dilemma in prescribing drugs in pregnancy really--which, I guess, has been touched on but not really addressed. And to follow up on the comments of the speaker from the public sector, would part of our discussion also be to maybe make a different kind of recommendation that we perhaps look at a registry first, but perhaps we really do

need to look at clinical trials and have the manufacturers consider that as a part of what we really need. Because we really don't have any data of any kind--as I think has been amply pointed out--and that perhaps we begin to look at these--I agree with Michael Greene: yes, we should look at all of the drugs, but maybe we should establish a hierarchy of the kinds of drugs, or the nature of the problems that we want to look at first, based on frequency, severity of complications, and medical necessity for exposure to the pregnant woman--or in the pregnant woman. There are certain drugs that I think are mentioned in the document and we're familiar with as practitioners of prenatal care and pre-conceptual care, that are really required for maternal well-being, and presumably for fetal well-being. If mother's compromised then the fetus will be compromised, and that's a problem in itself.

CHAIRMAN AZZIZ: Dr. Harris, let me just clarify. You were looking for a hierarchy of drugs? The draft document has a sort of a listing of potential drugs--pages 4 and 5--not a "hierarchy," in the sense of one, two, three, but it certainly has--following--it says, on page 4, "The following criteria can be used as a guide to evaluate the need for a pregnancy registry --" etcetera, and these are attenuated vaccines and NMEs and so on and so forth.

Do you disagree with that? Or would like to add

to that?

DR. HARRIS: Which--okay. Well, there may be some questions of--in the case of live attenuated vaccines, as to their necessity for exposure during pregnancy. I think, as Dr. Kweder pointed out, not so much with vaccines, but there are infectious diseases that do require therapeutic interventions during pregnancy. The question is whether prophylaxis would be necessary and whether there's even a role for exposure of the pregnant women to these live attenuated vaccines.

In general, I would agree with this approach and, again, I would emphasize those conditions that we associate--the necessity for interventions for maternal--for the well-being of the woman is the first category to look at, perhaps in centers where there's a focus of that interest, where you have a population you can look at in a systematic manner, so that you get some idea of what, in fact, the risk is of a new drug and, presumably, have some background information of what the prevailing risk is of adverse outcome for both the mother and fetus in that center, or similar setting.

DR. WEISS: Hi. I wanted to go back to that question about should we do registries for every new drug. And one of the things I wanted the committee to thing about is that registries are only one type of study design. And

we need to think about whether there will be adequate numbers of exposed women to have a registry from some drugs that may not be indicated for conditions that are common in women of reproductive age.

And we may need to think about the registries that are going on now, and difficulties with recruiting adequate numbers, even for conditions in which--that are common, when we think about that. So registries might not be the answer for every drug, and every question we have.

DR. CRAGAN: Jan Cragan--I'd like to add to that--some of the existing registries, the difficulties are not only with the recruitment but with the quality of outcome information--exposure and outcome information they get, and so the ones that are even functioning now have met with a modicum of success, at best.

I think, particularly if you're talking about assisted reproductive techniques, where you have that exposure very early under one caretaker, and perhaps management of the subsequent pregnancy under another caretaker, and then outcome of the infant, which comes from yet another practitioner, the difficulty in accessing sufficient information from all of those sources for one pregnancy--the confidentiality, and record access issues become pretty great for--at least the registries that have been set up currently.

So I think that's a--I mean, I agree that it's great to say we need to monitor all the drugs this way, but before you do that you need to look at how successful you can be at doing that. It doesn't make sense to spend a lot of effort doing that without generating the kind of information that will be meaningful.

DR. DATTEL: Bonnie Dattel, EVMS.

Two observations: one, I don't see how it's possible to go back and re-do every drug that's in--I mean, it would be a very nice thing to be able to get that information, but I just don't see how it's a feasible issue. I think we have to rely on people in research and pharmaceuticals, and academics and pediatrics and everything to provide information, and maybe with some guidance.

Secondly, also, I don't see how any drug--new drug--that would come on the market, with rare exception, could not potentially be used in a reproductive age person--I mean, especially since reproductive age is going up into the 50s these days. I don't see how that is possible, and to exclude certain drugs from Phase 4 trials, which I would think, if they're clearly going to be used pregnancy we would want those. But I think that there's always going to be that potential.

And those are just two observations.

DR. GREENE: I recognize--Mike Greene--I recognize

the problems with the quality of the data and the adequacy and completeness of the data, but I'm not sure that the ART situation is that unique. Women, for example, who receive psychotropic agents--those are usually prescribed by one provider, who is not the one who provides the pre-natal care, who's not the one who cares for the baby. So I don't think that the ART situation is that unique, but the issues with respect to data quality and completeness certainly pertain.

CHAIRMAN AZZIZ: I'd like to just remind the Committee, let's try to stick to the question of when a Phase 4 pregnancy registry may be appropriate. We'll move into ART drugs in just a second, because I think that they may have some more unique--any other comments on when a Phase 4 pregnancy registry may be appropriate? And I tell you that we've ranged here from "maybe we should think about it in all drugs," at least new drugs, to "perhaps we should establish a hierarchy," and then how do we do so.

I think that Dr. Harris' point, that perhaps there should be a hierarchy is important. The draft document has already some criteria for choosing those drugs for a pregnancy registry which are going to be new drugs. Again, none of this is mandated. This is all suggestions. I think those are very good. But there are obviously other drugs that have the potential for being used by reproductive-aged

women who may need, or should be advised to have a pregnancy registry. And the question is how do we choose those, among all the drugs. I mean, I think mandating all drugs is probably not going to be very effective, from both the kind of data that is being generated--as was pointed out--and the limitation of the data itself.

An example--and this is just an example for discussion--I mean, certainly one can attempt to estimate the number of women of reproductive age who may use this off-label. For example, hypertensive drugs will certainly be a much higher risk of being used, rather, than, say anti-androgens, perhaps.

So we do need to think of some method of establishing a hierarchy in drugs, even though they're not going o fit this--even though those are drugs not intended for women of reproductive potential, as we said earlier, there still is going to have a high potential.

Suggestions from the committee on ways to try to estimate this potential for exposure?

DR. TRUSSELL: I don't have a suggestion, but I have a question.

What did the authors have in mind as a definition of the word "common use?" 95 percent would certainly be "common." How about 5 percent?

CHAIRMAN AZZIZ: I'm sorry, Dr. Trussell--where is

"common?" I'm sorry--did you--

DR. TRUSSELL: Page 4, bullet two.

DR. RODRIGUEZ: We didn't have a particular percentage in mind. It was a sense that it would be not rare for women to be prescribed this drug for her own medical underlying condition.

DR. KWEDER: I actually can address that further.

You know, we--Dr. Weiss, when she was with FDA, did some work with us looking at, you know, what drugs are most commonly prescribed in pregnancy. And it's been done several times by several different folks, using management care databases, and looking at all prescriptions in women who are pregnant over certain periods of time.

We can identify those that are most common, but we also recognize that there are going to be products that may not show up in such databases, about which clinicians are concerned. We've done some work--actually several years ago sent letters to health professional groups and experts in neonatology and obstetrics, and asked them what do thing they're--what drugs do they think should be the biggest priorities for FDA to address. Sometimes they're not frequently prescribed, but they may be perceived as drugs about which information is important to have.

So while we didn't have a specific definition of "common," we need a definition that broadly allows us to

encompass drugs that may for one reason or another, be considered important.

I can give you an example. There is a pregnancy registry that's an interesting model of an industry consortium, that Dr. Cragan's very familiar with, which is the antiretrovirals pregnancy registry. There's seven companies that collaborate to collect data on women exposed to antiretroviral agents during their pregnancies, most of whom are taking--some of whom are taking the drugs solely to prevent perinatal transmission of the virus, others who are taking it for management of their own HIV disease, and then become pregnant.

In addition, that registry has collected somewhere in the ballpark of 800 to 900 exposures. We know that there are many, many more than that, and that it gets at some of the same issues that were discussed in relation to assisted reproductive technology. The average number of drugs that a woman is on at any given one time is three. Many are on many more than that.

In addition to that, there are other endeavors underway to follow up, long-term, infants who have been exposed in utero that are independent of the registry itself. So while these drugs are not necessarily commonly used, we recognize that they offer a unique situation. A registry may be appropriate for short-term outcomes, but in

addition, longer-term follow-up of infants, particularly those for whom the drugs work, and they're HIV negative, is important, and I believe the NIH, through the AIDS clinical trial group has an ongoing cohort study of infants who--of mothers who had previously been enrolled in a clinical trial that will follow these children out to age 18 to 20.

DR. TRUSSELL: I would suggest that if you meant "not rare," you say "not rare," because it creates a quite different impression than the word "common." If I were a company, I would want to argue that my drug is not common--25 percent is not "common," 30 percent is not "common"--"not rare," it would be harder to argue that 25 percent is rare.

DR. WEISS: Sheila Weiss.

One of the things I think was meant by the word "common," was if you look at the other categories, they were talking about drugs where there was suspected risk, or known risk that was going to be quantified, and what we wanted to make sure was in there is if there were drugs that were likely to be used in women, even when there was no risk suspected based on animal data or pharmacological data, if there was going to be a large number of exposed women, that the public health concern might override the lack of a hypothesis.

CHAIRMAN AZZIZ: I'm sorry--just--go ahead, Dr.

Lerner.

DR. LERNER: Hi. Jodi Lerner.

I just wanted to make a comment about outcome data, and I think that it's important, especially for those of use who do OB/GYN ultrasound to include the women who, for example, have major congenital anomalies early in the game--let's say a 16-week ultrasound, and then go ahead and terminate, based on that, that they still be included, even though they may not get to full-term birth, and then might be excluded in the outcome in the neonatal data.

CHAIRMAN AZZIZ: Just, again, a suggestion to keep the discussion focused: we're talking about different priority categories. Dr. Kweder has already mentioned that there has been some managed care/HMO databases which have been surveyed to see what different drugs are used. One suggestion for a hierarchy--one potential is simply to look at the incidence of the disease that is being looked at. I mean, diseases like hypertension, diabetes--these are going to be diseases that are going to have a high populational prevalence and, hence, a high prevalence of treatment; populations, for example--diseases which I look at--hirsutism and polystigovary syndrome--high prevalence diseases--again, 5, 6 percent of reproductive-age women--that is one relatively straightforward method of categorizing which drugs should be suggested to have a

pregnancy registry initially, by percentage--by incidence in reproductive-age women.

DR. HARRIS: I just had one question for Dr. Kweder.

In the HMO survey, if women are on two to three drugs, did that include prenatal vitamins, iron and calcium--

DR. KWEDER: No.

DR. HARRIS: --are they considered drugs, or--

DR. KWEDER: Sheila, correct me if I'm wrong, but we specifically excluded those because we knew they'd show up.

DR. LERNER: The only other additional category, then, is in addition to the sort of chronic medical diseases with pregnancy, or very common entities within pregnancy--certainly, urinary tract infections, respiratory infections, things that will be very common in our obstetric patient population.

CHAIRMAN AZZIZ: I think it would be helpful to modify the draft document to include a more clear list. There is a mention there of hypertensive disorders, and so on and so forth, but it is sort of lost in the text. And perhaps--it probably is worthwhile to either add a table, with a little bit more thought than what we're doing exactly right now, but add a table of those disorders or drugs that

probably need to do it. And then agree--I mean, not just drugs that are chronically medical; you know, the common anti-bacterials. I mean, how often do we give an antibiotic, which--sometimes with the newer antibiotics--to somebody who has a cold during pregnancy, and so on.

So those--I think a list--a more clear list--would be helpful in the draft document.

Any further comments on this? If not, let me just summarize what I think.

Anybody have comments--further--on this?

I'd like to--just to summarize briefly: we do think that certainly the suggestion for pregnancy registries should be the drugs that are not necessarily target toward reproductive-age women, but who may be used frequently by these women; establishing a hierarchy is going to be difficult, but it may involve drugs that are commonly used during pregnancy for other issues; and as well as drugs that have a high incidence in the population of women, in general, and those that are generally chronic medical diseases. There are some limitations in the data. We understand that, so we can't just apply it to all drugs.

I don't think anybody here has the feeling that we should go back and try to re-survey all drugs, but perhaps some of the drugs that fall into some of these higher categories probably need to be re-visited to see if they

actually require a pregnancy registry.

Any comments in addition to that summary?

[No audible response.]

CHAIRMAN AZZIZ: If not, let us continue with the second question.

The second question is: when is a Phase 4 agreement to conduct a pregnancy registry appropriate for drugs used in ART--as Dr. Bennett presented to us.

And I open the discussion.

[No audible response.]

CHAIRMAN AZZIZ: We had lots of discussion earlier about ART, and now we're--no comments, huh?

DR. LERNER: I think the hardest part, that's unique for ART, is that there's so much of the other extraneous stuff going on, in terms of the culture media, and the laboratory. So I think that that can be the first way to try and differentiate is the drugs versus the situations that have all the other laboratory stuff. And that may be a first--because I think the non-drug, you know, topics are going to be needed to be addressed, as well.

CHAIRMAN AZZIZ: I think--and this is just to start the discussion--as far as when should a Phase 4 agreement be conducted, I do think that any drug that is indicated for ART should have a pregnancy outcome Phase 4 registry. But the issue is, then--do you have a comment?

DR. FALK: Richard Falk.

I think the ART question is relatively easier than I think it may sound. ART, being a radically new and constantly evolving field, should have pregnancy outcome studies done, de facto, on ART. And in keeping with this, all of the drugs that are used in ART Will be included in such an overall study. So I think that the answer to this is there should be a Phase 4 agreement for all drugs used in ART.

DR. RARICK: Thank you.

I just wanted to clarify, and make sure that we're hearing your answers.

In the drug development for a product used in ART, we certainly have trials in which the patients--many get pregnant--fortunately--and then there's pregnancy outcomes that are known. We've got in the range of, you know, 200 or more pregnancy outcomes, at least at birth, but not long-term, for each of the products that's currently on the U.S. market.

What I'm hearing is that it seems commonsensical to this group to say, "But we need further information than simply the pregnancy outcomes at approval," and you would like for us to impose on each specific sponsor, that they open and run actively a prospective pregnancy registry.

Is that what we're hearing--and that you would

hold up approval of a new drug if a registry were not in place.

CHAIRMAN AZZIZ: In answering the question--and this is, again, what I'm getting the sense of the Committee--the Committee needs to respond--but in our discussion: yes, you're getting your impression correct.

These drugs are used for fertility, they're used for reproductive potential. They have a significant number of progeny associated with the early use of these drugs, and if not immediately during pregnancy, certainly immediately prior to pregnancy. And so, yes, a Phase 4 registry should be utilized in all of these drugs with this indication--or recommended, however you want to say.

So I do think that that is--unless there's some disagreement on that point. And before we change anything, I'd like to see if that statement--if any of you all have a disagreement with that.

DR. RARICK: I got it again, sorry. We're you trying to get it? No. It was still blinking.

I just wanted to make sure that I understand, because when we think of pregnancy registries as they're described in this document, for a drug used to make women pregnant, it almost seems like you're imposing a continued clinical trial, if you're doing this prospectively.

I'm just curious how the Committee would see that.

It seems like you wouldn't want to know just--I mean, people are interested in the maternal outcomes in failed cycles; people are interested in the pregnancy outcomes. And if we're interested in prospective gathering of data, it seems like every woman given one of these products would have to be signed into a pregnancy registry at the--even before they were pregnant, essentially.

DR. DATTEL: I just--Bonnie Dattel--I agree that that is something that needs to be done, and I also concur with the issue of separating laboratory exposures from the drugs. But, as you know, it depends, I guess, when you define life begins. But, you know, the cells are there, and they're being exposed.

And the other comment I have is--I'm the infectious disease person at my institution, in pregnancy, and the antiretroviral data is a very good lesson, in terms of long-term follow-up, because many of those children are not showing problems until they're entering school age, in some of the original--in the initial data. Now, of course, there are many confounders in that data set, but long-term follow-up, I think, has to be a component. I'm not sure if 100 percent, or whatever, but some percentage of randomly chosen children should probably have a longer-term follow-up as well.

I don't know how you put that into it, but there

are some lessons to be learned from other exposures.

CHAIRMAN AZZIZ: Continue with this. I think that the sentiment is, yeah, that these drugs should be. There's a big difference between the pre-clinical, or the approval clinical data. I mean, we're seeing 230 pregnancies, 72 pregnancies in the data that Dr. Bennett approved. I mean, we look at the ART labeling, which we've got here, and it's, you know, 215 pregnancies. This is a minuscule amount of data for approval. So I don't think that there really shouldn't be any kind of problem with registry data.

Now, the question really comes in--and I think it's very good--how long, and how much? And I don't think--I think we need long-term data, but we also may want to limit the number of pregnancies. I mean, there's a difference between long-term data and doing a registry that lasts 25 years. I mean, there's a big difference. I mean, if you collect x-number of pregnancies, or you say you follow 2,000 pregnancies, or 3,000 pregnancies--recommendation of number that comes from the statisticians, you can stop including patients in your registry at that point and just simply to continue to follow them long-term. But, certainly, I think there's a big difference in saying we want 20-year data, but that doesn't mean 20 years of patients data, it's 20-year follow-up

That would be my comment, and I'd like to

certainly have the Committee discuss that.

DR. HAMMOND: Well, I have a question about the utility of continuing to follow gonadotropin-type drugs. I mean, certain classes of drugs have been in use for 30 years, and I don't see why we would suddenly need to require a registry for a new gonadotropin, as a class, when we already have 30 years of data on use.

I can see that for new drugs--particularly new molecular entities--but for old, well-established medications--I wonder.

DR. TRUSSELL: I have a further question--I mean, the field is changing fast enough that I would think it likely at least, that some new drugs approved today aren't going to be used 10 years from now. And why, necessarily, would one want to continue to follow a cohort of people when the outcome will be only of historic interest. It won't affect anybody in the future?

CHAIRMAN AZZIZ: I think Dr. Trussell's--and Dr. Trussell, if you can just say your name--but Dr. Trussell's comment and Dr. Hammond's comment are very good.

And just to comment for myself, I think that one of the problems is that we've never gotten good data on gonadotropins. All of it is hearsay, and we're flying by the seat of our pants. Now, mostly likely they're okay, but if we continue to take this laissez-faire attitude about

getting data, we'll never get data. I mean, if we try to second-guess ourselves and decide whether we're going to use a drug for 10 years, I guarantee you most companies, aren't seeing a five-year or ten-year usage, otherwise they would never be here. I mean, this is not the issue. They're trying to see a longer-term, large market.

So I simply don't want to discourage the use of a registry just because we've gotten the impression that this type of drug has been used before, because certainly the formulations--molecular formulations--are varying significantly than they were before. But that's a comment.

DR. TRUSSELL: Sorry--James Trussell, again.

My comment was really meant to ensure that there could be some kind of escape clause so that a company could be let out of this requirement if the drug is completely never going to be used again.

DR. DATTEL: Bonnie Dattel.

I would say that I wouldn't want to be out, because it may signify something in a certain class of drugs that's going to be useful for future approvals. So I think once a registry is started, and it's to be--you know, it's 10 years, say--that it should be completed, even if the drug is no longer used, because another drug, three years later--or it may be a change in the molecular structure--is going to be present. So I would think that it would still

be important.

DR. RARICK: I don't know if you would mind, Ricardo, opening to the floor. I know there are some industry representatives in our audience. If there's anybody out there who's having a blood pressure attack and would like to say anything, I just want to make sure they have that opportunity.

[No audible response.]

DR. RARICK: Nobody--okay. If they're not willing, we're just start requiring them, and they can't get approved without them.

[Laughter.]

DR. GREENE: I'd like to ask some guidance from the FDA staff people, in terms of precedent here. Certainly, pregnancy is unique in some regards, but it's not unprecedented to have concerns about the implications of drug exposures 20 and 30 years down the road. Certainly, for example, we're still using some of the chemotherapeutic agents that we used 20 and 30 years ago, and the implications of their use early in life, 20 years down the road, were not necessarily known when the drugs were approved. Whenever we worry about these things, the specter always is raised about DES, which did take a generation to recognize the adverse consequences.

What is the precedent, at the FDA at the moment,

in terms of worrying about long-term adverse consequences?

DR. KWEDER: We actually have percent in some other areas, particular--I think some examples might be Temoxifin, or other drugs where carcinogenicity is a concern. We often work closely with sponsors at the time of a product's approval to establish a system for long-term follow-up of patients, either in a long-term--you know, continued follow-up of patients who had been enrolled in clinical trials, or an independent registry or prospective outcomes study.

I think we have had much more difficulty engaging sponsors, where the outcomes of concern are related to pregnant women and babies. I think that's to be expected. Many sponsors are very, very reluctant to engage in any research that brings them into this domain of clinical medicine. And I think that while we have some sponsors who have been very forward-thinking, and done a lot of this, they are not the majority. And that's one of the reasons that we're even having this discussion. I mean, in some ways it seems like, "Why are we even having this discussion. It seems so obvious." I mean, that's been the tone of some of the comments that are made.

But that's exactly why. There are concerns about liability. And, frankly, sometimes folks would just as soon not know. And that's not an accusation. I think it's just

reality.

Now, we do have an example of a registry that was--this was one of the first pregnancy registries for an non-obstetric drug--the acyclovir registry, established by Burroughs-Wellcome many years ago, and that registry recently closed because they had a substantial enrollment, and they had such a low adverse-event rate in the registry itself, that they realized that they would never be able to--given what they had to date, there would never likely be enough further exposures to document anything more meaningful than had already been discovered. And they worked with us to negotiate that, and what else was going to be done in its place.

So, yes--registries don't necessarily go on forever, but I think the point about, you know, thinking in advance about what the criteria might be for calling an end to it is an important point.

DR. GREENE: Mike Greene.

Please correct me if I'm wrong, but it seems to me that since the mid-1960s with the Goldenthal guidelines, some information with respect to reproductive consequences of all drugs, whether they're intended for us in pregnant women or not, has been required of manufacturers prior to obtaining--I believe it's an INDA, right?

DR. DATTEL: I think what's required is animal

data--it's animal data. Yes.

CHAIRMAN AZZIZ: Any comments from the public?

[No audible response.]

No.

Further comments from the Committee in regards to--we need to sort of summarize our sentiments, even though our sentiments are little bit varied.

Initially, we began with the fact that at least for ART drugs, which is what we were discussing, that as ART drugs come to the market, or--that we encourage the manufacturer/sponsor to continue pregnancy registries; how many individuals they register will really depend on a statistical estimation of what is required for detection of pregnancy--maybe a couple thousand individuals or so on; and then of course, that those pregnancies do get some long-term follow-up.

Now, an escape clause--if the company folds and disappears, I think there's always an escape clause there. If the drug--if they have had some exposure, then I don't think there's a lot of escape clause, because as we noted, there is a legal implication to this issue. So the companies, in fact, need to structure this well at the beginning to minimize that.

I think that would summarize our sentiment. Anybody in significant disagreement with that?

[No audible response.]

CHAIRMAN AZZIZ: Okay.

Let's move on, then, to the second question: If the FDA requires pregnancy registries for products used in ART, what types of information does the Committee recommend be collected?

What types of information--now this can be fairly massive, as anybody who's done anything with SART ever knows. And the question is: what is essential for information?

[Pause.]

CHAIRMAN AZZIZ: Dr. Falk, I'd like you to start, since you have the worst--best experience with SART.

[Laughter.]

DR. FALK: Well, I think we've really been talking about that all morning. I think you have to look at the early complications, at least as far as the offspring are concerned--the early complications. And then I believe that there should be at least a sub-set that is followed for a prolonged course.

I think the question of monozygotic twins is very important, at least with some of the manipulations; whether that has to do with the drugs or not, I don't know. I don't thinks so--but--and these are many questions that are already being--the early ones certainly are already being