active ingredient. It includes the excipients. The formulation, the safety, the unsafety of some of those particular excipients in particular populations is considered and is, in fact, usually communicated in the label as part of the product, the overall risk.

DR. KWEDER: In fact -- This is Sandra Kweder, FDA -- our pharmacology people are often -- They're quite meticulous about requiring that the formulation being used in the reprotox, say, or other tox studies is quite similar to what will be marketed.

Otherwise, companies sometimes get sent back to the drawing board, because we do need to have that information. We think that's very important.

DR. TAYLOR: Alan Taylor, Gilead Sciences.

It's clear that we're going to continue to have a heavy reliance on the animal data in describing risks to patients. I was glad to hear in Dr. Morse's discussion this morning that there is going to be a more global evaluation of the data in terms of the risk assessment.

I was wondering if there were plans to integrate more of that information into the labeling

beyond just what the findings are and what the exposure levels are.

DR. DeGEORGE: Well, if that's a recommendation, then we will do it. I think we intend to actually try to put as much of the information that leads us to the conclusions in the summary evaluation of the risk in the label. If that includes data from pharmacology studies, metabolism distribution studies, if that's critical in leading to that, hopefully that will be part of that section, so someone could actually flow from the data to the conclusion that we draw or to a different conclusion, as they find appropriate.

CHAIRMAN GREENE: Dr. Wisner had a question.

DR. WISNER: Whenever we give a drug to a pregnant patient, it's always because of a particular indication. So it seems to me, when we present this information about outcomes for drug use in pregnancy, what we're really presenting is outcomes that are potentially due to a drug but also potentially due to the maternal disorder for which the drug is being

used.

I wonder if, where there are data available, there is any thought to a section, helping the clinician separating out the risks of the maternal disorder untreated in pregnancy with the confound of the drug itself.

DR. BEHRMAN: We actually ask you this question this afternoon. It's something we're very concerned about, how to provide that context, the untreated pregnancy or -- so simply the risk of the pregnancy from the disease, how you separate that out, and how you would most like to see that information incorporated.

CHAIRMAN GREENE: Dr. Briggs.

DR. BRIGGS: A question for the FDA. Excuse me, Gerald Briggs, Long Beach.

Would the patient get better information, the clinician get better information if they used non-human primates for fertility and pregnancy testing rather than rodents?

DR. DeGEORGE: One of the problems, of course, is how predictive the animal data is or the

human data that we have anyway. I mean that, in trying to actually specifically say this effect correlates directly to humans from a rat, from a rabbit or from a primate. But there are additional problems in using primates in that you actually -- if we get very small animal numbers or numbers of pregnancies exposed in the testing from using rats and rabbits, the exposures that we would get from primates would be even many, many fewer. It would take a lot longer to generate the data.

We tend to rely on that only in those cases where we think that that is the only appropriate model to use, and we do use them in those settings. I believe for some of the antiviral products, primates were used because of particular concerns, in addition to the other animal models.

DR. KWEDER: We also -- I mean, we're pretty liberal in asking for specific animal models where we think the metabolism of the drug, for instance, is most similar to human metabolism, metabolites may be similar, those sorts of things.

Another example that we're doing that's

not pregnancy specific, but it's certainly related, is we are increasingly asking for the use of juvenile animal models in anticipating toxicities in pediatrics.

We've done that for the fluoroquinolones, for example, where some early studies of Cipro showed arthropathy in young dogs, and that's become standard, and we're doing it increasingly for other products as well where we think a juvenile model may be more appropriate.

You could easily see how we might extrapolate that to neonatal issues, which may be just as important for the pregnant woman who is being exposed late in the third trimester. You know, we have almost a term baby. We're talking about a baby, not a fetus anymore.

So those kinds of things do -- we do take those under advisement and try to apply the requirements rationally.

CHAIRMAN GREENE: Well, it is Noon. I would like to thank everyone for their presentations and the lively discussion.

We have one announcement before we break for lunch, please.

MS. TOPPER: You will be pleased to note that in the afternoon you don't have to identify yourself. By now everyone knows who you are.

The second thing is we do have a table reserved downstairs. They will hold your chair until ten after. After that point, it's given to anyone who walks in. So Angie will lead you down. She's the young lady in the beautiful green pants suit outside.

(Whereupon, the foregoing matter went off the record at 12:03 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:09 p.m.)

CHAIRMAN GREENE: We'd like to reconvene the meeting, please. This afternoon we have an opportunity for comments, and at least three people have requested permission to speak.

The first person I would like to recognize is Cynthia Pearson, please.

MS. PEARSON: Thank you. I am Cynthia Pearson. I'm the Executive Director of the National Women's Health Network.

As some of the FDA staff know, the Network is a nonprofit, science based, consumer advocacy group. We voluntarily do a financial disclosure every time we speak, in hopes that it will lead the way for others who come and speak during the public hearing to do a scrupulous financial disclosure.

We do not accept any financial support from pharmaceutical or medical device companies, and have no financial ties to any company or health care provider involved in pregnancy services. We are supported primarily by our membership, which includes

12,000 individuals in 300 organizations.

We are very concerned about the safety of drugs prescribed to women. We are 24-years-old, and in our founding year were invited to testify before the Senate on the use of diethylstilbestrol which, even though it had shown to be associated with long term harm to -- at that time the evidence supported long term harm in the daughters who were exposed as fetuses when their mothers were given this drug during pregnancy in the Fifties and Sixties and early Seventies, it was still being prescribed for other uses to women with the potential to be pregnant.

We rallied even before we had our formal organizational structure all worked out to let opinion makers and decision makers know what a burning issue this is to women, the potential harm that can come from drugs used during pregnancy.

As we've existed over the last 25 years, we've continued to work to ensure that women are provided the most accurate and complete information possible about drugs prescribed to them at anytime and also during pregnancy.

We are appreciative of being asked to -- or given the opportunity to participate today. Unlike the committee, we didn't see the concept paper until this morning. So we are very appreciative of your flexibility in allowing the public comment period to come after that and appreciated being treated with respect in that way.

We also have had a chance today to look at the questions you are being asked specifically this afternoon. So even though I've come with prepared testimony which I'm glancing down at and reading, I'm also going to try to weave in reactions to the concept papers which we saw after we wrote our testimony, and some comments in anticipation of the discussion that you're having later this afternoon, and I'll leave copies of the pre-prepared testimony. I know FDA staff are happy to get that into the transcript.

What our main points are is that we want you to remember, as we know you are making valiant efforts to do, but we want to help you remember and sharpen that issue for you even a little more, that this label is and will be used by women who are not

medical professionals, that whatever you believe is best to craft for an audience and in a setting which is primarily medical consumers, please remember that consumers are using this information as well.

Our second point is that what you call -- what you have termed relevance in some of the discussion this morning is something we feel is very -- It goes to the philosophy, the philosophy of the label in general and how that philosophy, we believe, should be slightly different in the pregnancy, fertility and lactation section, that the philosophy of the label and the philosophy of scientists and to the way in which you use the word relevance is that we should -- we, a scientifically based community, should be very careful not to impute causality until it's been proven, that we should not infer that harm shown to occur in animals will occur in humans unless that's been proven.

The question of relevance has come up over and over this morning, because in very few cases in the drugs that are being talked about is there anywhere near proof. DES, thalidomide, acutane are

some of the few where we've actually got very solid proof. But women considering pregnancy or finding out that they've been pregnant for a while have an understandably different standard of proof.

They have a different philosophy in approaching. I probably was wrong to call it specifically a standard of proof, because I think women can understand that, while they might use a different standard of caution in the absence of proof of causality, I think as the organization we represent, we believe that's a very reasonable decision for a pregnant woman to make, to try -- rather than to hold as the most scrupulous proof, we will not acknowledge causality until it's absolutely proven to swing the pendulum the other way and to believe for herself that she is not going to accept reassurances of safety unless there is a lot of proof.

If there isn't a lot of proof, she's going to at least consider avoiding exposure, even if it's exposure to agents and drugs for which there is no proof of harm, and she is going to make that decision about avoiding it, balancing not only the factual

information about her medical condition for which her clinician is recommending treatment, but the values she brings to the meaning of that condition.

Why I emphasize that is that leads to the third point that I wanted to make in reacting to the discussion that you've had so far this morning and the draft concept paper that we've seen, that the proposal which has already somewhat been struggled over amongst the committee of having a clinical management section come -- first of all, be included at all, and secondly, to be right up front, very up at the top above the risks.

I think our perspective from the consumer community is that that puts into absolute terms a value decision or a value weighing that comes from the professional community's standards, that we assume that the woman who is considering using this drug has the condition for which it's indicated and then here is the balancing of the impact of the drug on the condition versus the not full knowledge of risk that we have, and with that balancing here are the recommendations for clinical management.

It doesn't seem to us that that takes into account the meaning to the woman of treating the condition for which the drug is indicated, and that because we need to respect the values and the different decision making processes that different women will bring to it, that that's better to occur in a more individualized setting, in the one-on-one conversation with the clinician, and that putting it into the label in a sense almost reifies it.

It makes it a government pronouncement, which I know it isn't. You know it isn't. We know what the labels are, but for the person who doesn't interact with the FDA a lot, this is the government's decision and recommendation.

We want to respect women's decision making as more in an equal partnership. So those are the key things we wanted to communicate. Then going back to the testimony we prepared in advance, we would say that we're not an advocate of keeping the old categories, and it doesn't seem like anyone else is. So that's great.

It's great to be in consensus on that, but

unlike apparently where the thinking is at the moment, at least within the FDA and the working group, we like categories, and we think consumers like categories, and we think you even heard to a certain extent that physicians and focus groups tell you that they like categories.

We like tampon labeling. We like sunscreen labeling. It's easy. There's a reason why 30-15-9-4 stick in people's minds for their sunscreen or the tampon labeling system works. So we are here to recommend, even though it sounds like -- If I were a staffperson, I would be wincing, because it sounds like it will take you backwards to where you feel like you've moved on from.

We're recommending that you do keep a system of categories and, if it were just to be transposed on top of the draft concept paper you showed this morning, the categories would be attached to the summary -- risk summary assessment. I'm not sure I got those words in the right order.

Our recommendation is that the categories be used to reflect the type of knowledge available on

risk, and that categories be ranked from one to five with one being the best -- that's sort of just bringing the cultural use of numbers into this -- and that one, we acknowledge -- category number one would be used very rarely, because for us category one would stand for that the level of evidence means the drug has been studied for its effects in pregnant women and their fetuses and that research data indicate that it is safe.

Now we opened up this morning with someone saying from the FDA there's just a handful of drugs like that. Category 2 would be that it has not been studied for safety in pregnant women and their fetuses, but research data from animal testing indicate that it is safe for use in pregnancy in animals.

Now that may be the condition in which many new drugs or some new drugs would come to the FDA in. Then Number 3 is effect on pregnancy unknown, which from what we heard in our historical briefing is the condition, the state of which some drugs are in right now, that they were approved before that type of

animal testing was required.

Then category 4 in our recommendation would be harm shown in studies in animals, and category 5, harm shown in studies in women or reasonable reporting systems in women.

We acknowledge that part of the impetus towards this revamping of the system was the confusion of trying to intermingle risk and benefit in the old category system, and that leading to inconsistencies.

What our recommendation is, that we take that weighing of risk and benefit to some extent out of the label and into the individualized conversation between the woman and her clinician, and let the label serve for women as their reference point of just how much is known about the potential for risks caused by this drug and where is it known from.

I think those are all the comments I wanted to make, but I know -- Oh, I did want to just reflect briefly -- I know I've used a fair amount of time-- on the questions that you're being asked to respond to later this afternoon, and say that in terms of your question of referring the risks of the drug to

other risks in context such as the risk of pregnancy or the risk of the untreated condition, I think that's reasonable.

The larger reproductive health committee that you're a subcommittee of has made that recommendation in terms of contraception, that when you get your factual information about the effectiveness of contraception and any rare side effects associated with it, that you also get a comparison of the effectiveness of all contraception and what's the baseline level of those rare risks in that age group of women.

That seems pretty reasonable, and I think women considering the effect of drugs taken while they are pregnant would be happy to see that sort of information.

I think you're -- Apparently, you're going to be asked to give feedback on is it better to use qualitative or quantitative information about risks in this revamping of the labeling. It sounds like we heard this morning that you have to use both. I think that would be the Network's input to you.

I think also on your question about the goals of the discussion of data systems within the constraints of not making each and every label 17 pages long -- and they are already long, and they're already in fine print -- it sounds absolutely wonderful to have the sort of fairly lengthy discussion of data that you laid out in some of those draft mock-ups, where you really get into what kind of animals were used, how large was the sample size in the animal studies, and what type of human experience has been reported on, if there's any information known from humans.

So now I'm really getting the signal to wrap up. So I'll stop, but I'll stay up here for just a second to see if any of you have specific questions for me. Thanks.

CHAIRMAN GREENE: Thank you.

I'd like to recognize Doris Haire, please.

MS. HAIRE: Good afternoon. The last time I was here before this committee, I was four days away from open heart surgery, which I knew about before I came, but I had asked my doctor if I could do this one

thing. So, fortunately, I don't have anything planned for a few days from now.

As President of the International Childbirth Education Association, Chair of the National Women's Health Network, and current President of the American Foundation for Maternal and Child Health, I am pleased that the FDA has concluded that the agency's pregnancy risk categories have failed to provide health care providers and, in turn, their patients with information that would improve the safety of drugs used in pregnancy, childbirth and lactation.

While I appreciate the FDA's addressing the issue of safety in regard to fertility drugs, I believe that it is essential to create a separate category for drugs used in pregnancy, childbirth and lactation. The inherent risks of drugs administered during organogenesis is not the same as the risks of drugs administered during childbirth.

The reality is that none of the drugs currently being administered to women during pregnancy, childbirth and lactation has been subjected

to large, randomized controlled trials that have attempted to follow up on development of the children exposed in utero to the various drugs regimens. Without such a follow-up, the FDA has no idea if the possibility of fetal harm is remote or whether it's perfectly fine, but we have no way of knowing.

I just spent three days with almost 1,000 obstetric anesthesiologists. That's an accomplishment in itself. But I was amazed at how much effort is being done now by anesthesiologists to market their wares.

One of the speeches that was given was talking about the fact that in one obstetric anesthesia service they had nurses working around the clock to talk to the patients, to educate them to the benefits of epidural. So we are in for a major impact, I think.

A recent review by DeLorier, et al., showed that outcomes of 12 large, randomized controlled trials had not been predicted accurately 35 percent of the time by the meta analyses published previously on the same topics. Our experience with

thalidomide has taught us that animal reproductive studies are not always predictive of human response.

I find it disturbing that the FDA in general is not willing to admit to the public that none of the drugs intended for use in pregnancy, childbirth and lactation has been subjected to a properly controlled scientific evaluation.

Why is the FDA so reluctant to advise the public that only those doses and conditions noted in the Indications section of the package insert are FDA approved uses of the drug, and that if the words pregnancy, obstetrics, birth or lactation are no in the Indications section of the package insert, then the drug has not been approved by the FDA for treatment of those conditions.

I'm anxious to know whether or not the Indications section will remain in the package insert.

While European perinatologists and WHO call for large, randomized controlled trials to evaluate the safety of drugs to be administered during pregnancy, childbirth and lactation, the FDA seems more intent on maintaining the form of care based on

physician practice patterns rather than science.

Even though the FDA publication, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children," has not been updated in a quarter century, it at least acknowledged that in pregnancy, labor, birth and lactation there are two patients, distinctly different, with unique vulnerabilities.

It is time that the FDA stops thinking of drugs in pregnancy and childbirth as posing a risk only to the mother. Women are far more concerned with potential risks of a drug to their infant and child than they are on their own wellbeing.

A normal PH and heart beat at birth do not mean that the infant has come through the birth process unscathed. A drug induced drop in fetal heart rate cannot be assumed to be benign.

Research by Mallard, et al., carried out in animals has found that even brief periods of oxygen deprivation can cause damage to the hippocampal region of the offspring's brain, even though there was rapid recovery of other potential indicators of fetal

asphyxia. Mallard also noted that, after the apparent recovery, there was often a subsequent progressive decline in neurologic function.

Drugs administered to the mother are in the fetal blood and brain within seconds or minutes. Recent research by McCann, et al., have shown that a drug's effect on the brain cannot be assumed to be temporary.

The manufacturer of promethazine, a drug frequently administered during childbirth, cautions in the package insert that the drug can disrupt platelet aggregation in the fetus. Then Corby points out that such an effect can cause bleeding within the fetal brain without similar effect in the mother.

Behavior scientist Joseph Altman warned several years ago that drug induced alterations in fetal brain chemistry may interfere with the synchrony of cell and nerve fiber growth, causing subtle or gross misconnections within the developing circuitry.

Yet what has the FDA done to determine if such bleeds disrupt dendritic arborization within the rapidly developing brain of the fetus? This is still

one of the most commonly -- Phenergan is the drug, a brand name -- and it is still one of the most commonly used drugs in the United States.

In 1977 the U.S. Food and Drug Administration acknowledged that drugs trapped in the infant's brain at birth have the potential to affect adversely the rapidly developing nerve circuitry of the brain and central nervous system by altering neuronal maturation, cell migration, dendritic arborization, and myelinization.

Not long after that, Donald Towers, who was then Director of the National Institute of Neurological and Communicative Disorders and Stroke, said, "It is the biochemical circuitry, the biochemical messengers and relevant nerve cells in the brain, that form the basis for mankind's behavior."

The work of Zheng reported in the May 13, 1996, issue of Science supports the words of caution by Tower, Altman and others by showing that the migration of neurons along the glia fibers within the bran can be altered by the normal chemistry of the rapidly developing fetal brain.

It would appear that, at no other time in an individual's life, is his or her brian more vulnerable to drug induced alteration, trauma, and permanent injury than during the last hours of pregnancy and the early hours of life.

I was heartened recently when I attended a meeting on brain development at the New York Academy of Medicine. It was particularly encouraging to see the attention being given to potential behavioral teratogens such as oxytocin.

The FDA owes it to parents to make certain that the drugs used by and administered to women during pregnancy, childbirth and lactation are not behavioral teratogens.

There is growing concern in the U.S. that obstetric related drugs contribute significantly to our high rate of learning disability and deviant behavior. American children, on the whole, continue to lag behind children in most other industrialized countries in academic achievement, especially in those areas of education such as math and science that require comprehension and deduction.

In fact, at the meeting on the brain in New York, the final conclusion among the group was that one out of every five American children has some significant neurologic dysfunction.

American women are growing increasingly impatient with the failure of the FDA to adequately assess the potential risks to their offspring of drugs prescribed for and administered to them during pregnancy, childbirth and lactation.

I urge you not to jump out of the frying pan into the fire by coming up with new directives for package inserts that fail to delineate not only the known risks of a drug to be used in pregnancy and childbirth, but also the important areas of uncertainty in regard to the fetal and newborn brain.

Is there a reason for concern? Rosenblatt and later Sepkoski and colleagues have shown that the adverse effects of bupivacaine, used in epidurals, can still be detected several weeks after birth, six weeks and four weeks respectively, with no sure evidence that the condition was corrected after the testing period concluded.

To ensure that the FDA is making every effort to protect women and their offspring from drug induced injury, I propose that the FDA take immediate steps to require all manufacturers -- excuse me -- to require the manufacture of all FDA regulated drugs to include in the package insert the following sentence: In regard to infant outcome, there are no adequate and well controlled studies in drugs administered or prescribed for women during pregnancy, labor, birth and lactation."

The FDA should establish an interdisciplinary advisory committee, chaired by a pediatrician, to determine the effects of obstetric drugs on both the mother and her baby.

I have attended many of the meetings of the -- Let's see, it used to be called the Fertility and Maternal Health Drug Committee. I never saw a pediatrician. How can anyone deliberate the safety of drugs without pediatricians?

I also think that's true for midwives, because midwives are the only one that can produce consistently drug free controls.

There are many things. Let's see. I'd like to urge Congress to fund a second updated Collaborative Perinatal Study, chaired by a pediatrician -- you can tell I have a certain appreciation for pediatricians -- which would gather data on maternal and infant outcome for births occurring in a single week in selected hospitals, as done in the U.K.

The idea of the collaborative perinatal project -- It was sort of a disaster, because it went on too long, and everyone I know tells me they cheated. I mean, they weren't about to get up in the middle of the night to do an Apgar.

I'd like to see that the FDA require manufacturers to provide women and men with the package insert of the drugs they are offered, and then publicly encourage women to read the package inserts and discuss the information with their providers before deciding whether or not to take or forego the drugs offered to them.

Thank you.

CHAIRMAN GREENE: Thank you.

The chair would like to recognize Dr. Robert Brent, please.

DR. BRENT: Doris, I was a pediatrician on the Maternal Health Drug Committee. It was a long time ago, though.

Thank you for giving me the opportunity to speak with you today. The Committee has a very hard task, and I'm not here to tell you what to do, but I would like to make some comments about some of the things that were discussed.

Actually, when I was on the Maternal Health Drug Committee, there was never a time at the FDA that exciting things are not going on, as you know, and we were discussing at that time bendectin and sex steroids, oral contraceptives, clomiphene, vaginal sponges, and there's always controversy. So that's not going to stop.

At that time I actually made a presentation to the FDA about the fact that I felt that the categories were misleading and produced bad medical results by women aborting pregnancies because of misinformation provided by their clinician, and

that was a thing that concerned me at that time.

In 1982 I wrote an article about eliminating the categories that was published in one of the pharmaceutical journals.

I'm interested in this subject very much. I was here -- I think it was September 12th a year and a half ago. It was a very interesting meeting and very elevating, and these are my comments.

I happen to be an animal teratologist. Unfortunately, I also do a lot of genetic and teratology counseling, as Dr. Jones does and some of the others here. I would say that our perspective on some of the comments that were made here are quite different.

Number one is, it's very hard to give a generic explanation that will apply to every patient, and especially I am somewhat offended by thinking that, because an obstetrician says he wants a one-sentence, bottom line to be able to tell his patient, it would be like he would want one instrument to be able to do all his surgery.

The fact is that you can't simplify some

of these things. If the patient has got one religion or another or she's got two other children at home or she's got a malignancy, on methotrexate or she's a rheumatoid arthritic on methotrexate, it makes a big difference what you're going to tell her.

So I'm concerned that we think we can simplify the kinds of things that you can say in a little package insert that's going to apply to a large group of patients receiving that medication.

Now with regard to the animal studies, back in 1964 I wrote an article about upgrading the method of doing animal research, and two things that I've said then and I've said ever since that are just beginning to be adopted are that, while we go to maternal toxicity in animal studies, that's irrelevant.

You know, because you can kill with a drug and maybe get some birth defects at 1,000 times the therapeutic dose, it's something that we report in the NDA or the preclinical studies. What I would rather like to know is what is the no-effect level? What is the blood level at the no-effect level in the animal,

and what is the blood level in the human being getting therapeutic dosages?

If I knew that the blood level in the animal before you got any reproductive effect was 100 or 50 times greater than the blood level in the human, that would be very helpful for me to do risk assessment, much more important than, you know, the fact that you get these effects at these dosages much greater.

So I would like to see studies that are in the range of the pharmacokinetics of human exposures and at the level where we get no effect in animals.

The second thing is that malformations are not the same. You know, you get somebody saying, oh, there was this malformation with this drug. It makes a big difference what malformations you get in animals.

We have a phenomenon in teratology called epigenetic effects, cleft palate in the mouth, limb defection in the rabbit, cleft palate in the rabbit, encephaloceles in the mouth. Those are all genetic diseases that occur in a small percentage of many mice

and animals.

With maternal toxicity, you can bring them out. It has nothing to do with the teratogenic effect and absolutely nothing to do with its relevance to human studies. I think that's important when people are making these interpretations about risk assessment.

I saw for the first time that very complicated chart with the numbers, and I don't like to second guess people; but I have some suggestions. What I would like to see you do is to take that chart -- and I really couldn't see it from where I was. I would take that chart, and I would take ten drugs that we know most about, bendectin, sex steroids, dilantin, the cancer chemotherapeutic agents, and I would do away with the human studies and just take the animal studies and see what kind of numbers you will come up with those, and see how closely they line up.

If you get something like bendectin and some other drug that's a nonteratogen and they come up with the same numbers, and you can show that the methods that you have work with known drugs that

you've got a lot of epidemiological data, then you can begin to say let's try it on drugs where we don't have any epidemiological data and look at the animal data and get experienced animal people to look at the data and come up with a consensus.

I think we would learn a lot if we used that methodology.

Let's see. I mentioned about the sampling of physicians. I thought that was a very interesting study, but I can tell you from my own counseling, many of the patients call me, because the obstetrician doesn't have time to talk to them. He doesn't want to spend -- You know, it's not his fault. HMOs don't pay you for talking to patients.

I don't get paid for doing this, but I like to do it, and I, therefore, relate to the patients. But the fact is that, because you sample physicians and they tell you what they want, it doesn't mean that they know what they're talking about. That's what concerns me.

So I really would like to see people who do this all the time day in and day out -- and I get

a lot of calls from genetic counselors who are confused about the data, and even from Dr. Jones' laboratory on a specific subject, and he's got good people there.

So you need people knowledgeable in all these areas to come up with information about risks; and if you have to do it with just animal data, you need experienced people.

Finally, I think Dr. -- This is a very important point. Patients never call and say I took this drug, I'm worried about stillbirth. I've never had a patient say that to me. They're interested in malformations most of the time. That's what they're interested in.

They don't want to know whether the child is going to have interuterine growth retardation, whether the child is going to be stillborn or whether she's going to be infertile. So that the primary thing that concerns the patient is the malformations.

The second thing is that I would say this with regard to communicating with the patient. It's very important -- Sandi, you brought this up. You

need to tell them what the spontaneous incidence of the disease that they're talking about is.

It's much more helpful, and that's the hard thing for a physician. You know, I hate to tell a mother that she's got a three percent risk of having major malformations.

It's very, very difficult to tell a woman who -- You know, if she hadn't called you, she would go through that pregnancy and have a 97 percent chance of having a normal baby and never have raised the issue to promote anxiety all that pregnancy. But once she calls you, you've got to tell her what the risk is.

Then you can tell her, you know, what the -- based on the animal studies and, of course, that's all you're going to have with these new drugs -- that the risk -- You can tell her what you think the risk may be with regard to the human studies -- with regard to the ordinary incidence of birth defects and these other things.

I would be reluctant to, in the package insert, talk about all these other things except the

malformations, at least in the beginning. But I'm going to stop here, and I'll tell you why.

You've got a lot of work to do, and you got to practice about doing these things, and you got to have a lot of people look at what you're writing. I think, altogether, we can come up with something that's going to be beneficial to the public and to the FDA.

Again, those of you who don't realize how hard it is for a regulatory agency to change direction or change procedures or develop new regulations, it's tough. It's tough. Everybody has got criticism for them, and I just want to compliment them for this effort.

CHAIRMAN GREENE: Thank you.

If there are any other public comments, we would like to recognize you, please.

DR. GIACOIA: I am George Giacoia from the National Institutes of Child Health and Human Development. I have a very short comment.

I believe that use in the FDA lingo the name of the subcommittee is mislabeled. It is called

Dependency Labels, that committee. I think more appropriate will be the partial labeling, the Pregnancy Subcommittee, because you are not dealing with efficacy.

I am thrilled to learn that members of the subcommittee of perfectly aware of the tremendous changes imposed by the pregnant state on the deposition of -- in pregnancy and the need to do a status of -- in pregnancy.

The FDA needs to be congratulated for the extraordinary efforts that they have made for pediatric labeling, but those efforts didn't happen overnight. Actually, it can be traced back to 1991 at a meeting at the Institute of Medicine with representatives of FDA, NIH, academia and industry.

There the first seeds were planted, and among them was an incentive program that crystallized in the pediatric provisions of the Food and Drug Administration Act of 1997.

So I like to believe that Sandi Kweder is wrong when she states that this will never happen. I think that the public will recognize this as a public

health issue, that pregnant women will not be discriminated against. After all, it's only an issue of money, which is much simpler than the task of dealing with the tough scientific problems related to safety. Thank you.

CHAIRMAN GREENE: Dr. Christian.

DR. CHRISTIAN: You have a very difficult task. There are a few things, though, that I'd like to congratulate FDA on doing.

One is on the intensive training that they have been giving the reviewers. I think this will be very, very helpful in allowing the data and in working with the pharmaceutical companies in making the data presented consistent and appropriately interpreted.

Now a very large problem is the problem when there is only animal data available. I'd like to emphasize one thing that Dr. Brent said and sort of refute another thing.

One thing that he said is that it would be very important to look in the target dose level -- what I'm talking now is the serum level, the target dose level of drug that is actually administered and

obtained in the animals -- and compare that with that used clinically.

I don't know the appropriate multiple. I'm sure that that's one of the most difficult things that the committee has to do, because they have to say is a 5 good, is 100 good, is a tenfold multiple good or is the drug so safe even at the same level that is clinically used, it's safe to do? That's an extremely difficult problem.

I think that that information certainly should be included and used consistently in the labeling.

The other thing is we've come so far in no longer identifying malformations as the only thing that is important that I think it's very important in looking at those blood levels comparatively to identify whether any of the standard effects that we evaluate in animal studies -- I'm talking about only the effects on development; I'm not talking about the reproductive effects that may be due to parturition or lactation, but the in utero effects that we can see how an embryo responds.

It can die. It can be small. It can be functionally deficit, not only in CNS, or it can be malformed in some way. Certainly, our scientific advances are going from malformed enzymes structures and gene changes all the way up to gross external malformations. But in consideration of that, look at multiples for human use that are safe based on all of these endpoints; because if we know one thing at this point, it's that scientifically we do not yet have the ability to specifically identify a particular change in the animal system to a particular change in the human.

We always use the example that we still don't know the mechanism for thalidomide. That's absolutely true, but had we done the animal studies appropriately and looked at it, we would have seen the animals respond, and we could have looked at other outcomes; but we chose to eliminate rat studies with embryo deaths, because they weren't malformed the same as humans were observed.

With valproic acid, we discovered it in humans, because we chose to ignore other

malformations, retarded growth, delayed development of other systems, changes in the CNS development in the animal systems, because they were only animal studies, because they weren't the same, the exact same thing as occurred in the human system.

So that's all I want to add, is that caution. Do not directly extrapolate, but consider all the normal four endpoints and look at the other reproductive processes that may also be affected, and perhaps most important, consider that in terms of the background and the clinical use of the agent, which I know you do all the time.

That's so important, because it's so often that we look at human cases. We see an animal case, and we pull that animal data out, and forget everything else that has happened in the clinical situation.

I really congratulate you on all the progress you've made in the year since this committee has been working and the FDA has been working on this particular problem, and with you very good fortune in doing what is most difficult, in my experience, and

that is communicating with the general public.

Thank you.

CHAIRMAN GREENE: Thank you. Other comments? Please?

MS. HEISER: Yes. I am Barbara Heiser, and I am the Executive Director for the National Alliance for Breastfeeding Advocacy and a former La Leche League International board member. I'm also a registered nurse and an international board certified lactation consultant.

Because the U.S. has set up goals for our nation around the issue of lactation, I know it's talked about but very little this morning, in the need for information for women that are choosing to give the best nutrition to their babies via breastfeeding.

Moms are becoming more and more concerned about what happens when they take drugs, to the point that many of them don't even attempt to breastfeed their babies, because they know they have a thyroid condition and they're going to have to be on medication.

The drugs used during labor and delivery

that was talked about earlier has a great impact on the initiation of breastfeeding, especially with early hospital discharges.

We also have moms over -- I've been doing this for 20-some years, and the increase in calls I get on information about breastfeeding and drugs has just gone sky high recently. I'd say at least 50 percent of the calls I've gotten in the past two weeks have been drug related calls.

Mothers are afraid that their baby is going to get any of that drug. I want to recommend FDA for what they are doing, that they are noticing the importance of pregnancy information, but you must include lactation in that information, realizing that both the nation and the American Academy of Pediatrics has set a goal for breastfeeding for one year.

So that gives you a long time of information that's needed. Thanks to Dr. Briggs for one of the only sources of information we do have to use. The piece of information that's needed for the label is the plasma/milk ratio, is one that's really critical for it to be there.

I do, as a consumer, though, want to assure you that mothers are reading all of those labels, and that is a major problem, that you aren't just addressing the medical community, that more and more women are reading labels and are concerned about what they're finding.

I look forward to seeing increased information as you develop your standards. Thank you.

CHAIRMAN GREENE: Thank you. Any other comments, please? Okay. Seeing no other public comments, I'd like to move on in the program to the presentation by Dr. Francois Meyer on the European labeling initiative, please.

DR. MEYER: Thank you very much for the invitation. I'm Francois Meyer. I'm a physician by training. I've been working for the French Medicines agency, which is now called the French Agency for the Safety of Health Products, for two years now as a Deputy Director of the Medicinal Products Evaluation Department, and I'm here to speak on behalf of the European Committee for Medicinal Products, the CPMP, to give you some information on the situation on the

guidance concerning pregnancy labeling in the European Union and the CPMP initiative on this topic.

Next slide, please. I will not insist on the background situation before this guidance has been drafted or the drafting of this guidance has been started. It was not satisfactory, certainly, with information not addressing all the situations, and in addition to that, as of course, we have different countries, we have on the market products which have been approved through national procedures with different information from a country to another.

As you can see on this example, in 1993 for a beta-Sympathomimetic agent, the information was quite different from a country to another concerning pregnancy. In some countries no information was available. In another country it was stated that the product can be used during pregnancy, and other countries a product was not recommended or even contraindicated. So that's an additional difficulty in Europe.

In this situation, an update of the guidance of the summary of the product characteristics

has been started. So what is the summary of product characteristics?

It is defined on the first -- the second page, I think, of the document I have given to the members of the committee. It's defined in the regulations in Europe, and it is the information to be given to the physicians about the product, and it has to be approved by the competent authority.

It is proposed by the applicants in the dossier for the marketing authorization application, but it has to be approved by the authority, and it forms an intrinsic and integral part of the marketing authorization.

So the SPC is the basis of the information for health professionals on how to use the medicinal product safely and effectively, and it cannot be changed except with the approval of the original competent authority.

The patient information must be consistent with the SPC, but in a wording that can be easily understood by nonspecialists.

The SPC has not to give general advice on

the treatment of particular medical conditions, but can deal with specific aspects of the treatment related to the use of the pharmaceutical products or its effects should be mentioned.

So the guideline which is being drafted had to provide advice from the principles of presenting information on the SPC. Next slide, please.

So before dealing with the particular situation of the pregnancy labeling, I will just make information on the format of the SPC. There is a legal format for the SPC with Section 1 and so on, and Section 4 is for the clinical information of the products. Subsection 4.1 is for indications. Subsection 4.2 for pathology, and so on, and the section which deals with pregnancy and labeling is Section 4.6.

So that's mainly in the section 4.6 that the information on pregnancy will be found with some little exceptions that you will see later.

So focusing on the labeling on pregnancy, where are the objectives when we met on several

occasions at the European Medical Products Evaluation Agency, the MEA?

The objectives of the pregnancy section is to provide physicians with, first, a summary of the available, relevant information from, first, the human experience concerning pregnancy outcomes and postnatal outcomes, and secondly, the experimental data on reproductive and developmental toxicity.

From these data should be driven risk assessments which should be part of the section concerning the possible effects of the drugs on fertility and pregnancy, and information and guidance for the clinical or the risk management -- I mean how to deal with clinical situations, both aspects pregnant women or women of childbearing potential considering therapy -- so the prospective situation -- and secondly, the inadvertent exposure.

What format should be used for that? It has been discussed considering the drug categories. I think that those were the same in our side of the Atlantic Ocean and in the U.S., and drug categories were rejected as misleading, overly simplistic, and

we, of course, took benefit of the reflection and particularly the hearing on this topic that was held here in the U.S.

So drug categories were rejected, and a narrative text was preferred, to include as much details as necessary on the nature of the available information concerning human data and experimental data. However, if narrative text was preferable, the need for certain standardization of the language was highlighted in order to allow comparison between drugs of the same therapeutic class and to facilitate the choice of different products for the physicians and the patients.

How were considered experimental data? It was considered that experimental data should be considered as either positive, negative or insufficient. Positive where malformities or fetotoxic effects were shown in animals, and these findings were to be interpreted as a potential human risk to be discussed depending upon the particular study, and negative data from well conducted studies where -- in the case where no effect have been shown

in studies in animals which were well conducted and in at least two different animal species, including one non-rodent. That's the conditions to be -- for a drug to belong to the category of a drug with negative animal data; and insufficient when none of the previous criteria were met.

So how to use these negative animal data? We checked first before concluding that in another era of evaluation of the toxicity of products to humans, the conclusions were not different, and we noticed that in the U.S. your environment protection agency guidelines for developmental toxicity risk assessments, it is stated that for a substance for which no sufficient animal data are available, the minimum evidence to judge that a potential hazard do not exist would include data from appropriate, well conducted laboratory animal studies in several species, at least two, which evaluated a variety of potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adults.

So we are a bit in the same philosophy by

saying that negative animal studies, if they are well conducted, have a strong, even it is not absolute negative predictive values, and considering on another hand that drugs known to induce, for instance, birth defects in humans have demonstrated a teratogenic effect in animals, provided that well conducted experimental studies were available in two different species.

So it was highlighted that the negative experimental results should not be disregarded. It should be taken into account when drafting the pregnancy labeling section.

Concerning positive animal studies, the positive, predictive animal -- predictive value -- sorry -- of positive animal findings should be assessed very carefully; because values factors have to be taken into account. Some species are known to show birth defects which -- toxicity, for instance.

So it is very important to be careful when making a risk assessment from a positive animal finding.

So for that, one has to examine the

associated doses, routes,blood levels of the drug, timing, duration of exposures, and exposure levels is an essential factor for risk assessment, by comparing these levels with the ones expected in women and therapeutic agents.

So that's in animals. Concerning human pregnancy, we considered that there were drugs for which thee was a known or suspected risk in humans. So either malformities like thalidomide or fetotoxic effects, drugs for which no relevant information was available.

In this category we would put drugs with a long presence on the market but no relevant data available, considering that a long presence of the market was not sufficient to be considered as a safe results, and drugs for which no particular risk were shown in some human data available, but with a distinction with drugs for which there are limited human data and drugs for which there are more reliable, more extensive and epidemiologic studies available.

The figures on this picture are just

indicative, and there is no consensus yet in Europe concerning the numbers, for instance, of in the K series the number of pregnancies which should be taken into account to indicate if there is limited or more important data available. We will go back to that later.

So this busy slide is just shown to demonstrate that from these data, the human first and, second, the experimental data, because human data should prevail over experimental findings, the risk assessments and risk management is established. So that's by combining the information available in human and in animals, we can obtain these standard statements which, of course, have to adapted to every single case, every single drug.

So that was the way we started to deal with the problem. Where are we now? So we are now to the nearly final but not yet adopted draft guidance on SPC, which is global, which deals with all sections of the SPC, but what is written in the SPC guidance concerning pregnancy, because pregnancy can be mentioned in the section 4.3, contraindications, in

case the drug is contraindicated in pregnancies.

The main information is to be put on the 4.6 section, Pregnancy and Lactation. These words are the exact words of the draft guidance. So this section should mention concerning pregnancy first. So the facts on human experience and conclusions from preclinical toxicity studies which are of relevance for the assessment of risks associated with exposure during pregnancy.

Recommendations on the use of the medicinal products at different times during pregnancy in respect of gestation, recommendations on the management of the situation of inadvertent exposure where relevant, and guidance on the wording of this section is given in an annex which is called Annex XX.

if there are some very detailed information concerning preclinical toxicity studies, they should be given in another section, which is Section 5.3, which deals with preclinical findings.

Concerning -- So the section 4.6 should deal with the question of women of childbearing potential. Recommendations of the use of the

medicinal product in women of childbearing potential should be present when appropriate.

Finally, lactation, information on expression of the active substance and/or its metabolites in milk should be given; and where relevant, recommendation as to whether to stop or continue breastfeeding should be given.

Concerning fertility, the guideline states that information regarding fertility should be given in other sections. That means Section 4.3, contraindications, 4.4 special warnings and conditions for use, 4.8 under the --; or 4.3, preclinical safety data as appropriate.

I must say that we are not very happy with that because, of course, it spreads over various parts of the SPC the information on fertility, which is probably not very satisfactory. So this could change very soon.

So, finally, going to the annex where some wording examples are depicted, we finally agreed on four grades of so called recommendations for drugs, depending on the data available in human and in

animals.

The first should be trade name is contraindicated in pregnancy. The second, trade name should not be used during pregnancy unless clearly necessary. The third one, caution should be exercised when prescribing to pregnant women; and the last one, trade name can be used during pregnancy.

These recommendations correspond to values -- level of information available from human and animal studies, and maybe -- Could I have the next slide. We are going to see each of these eight situations, one after the other.

So the first situation is when a drug is suspected or causes birth defects during pregnancy, and in this case the drug is contraindicated, and women of childbearing potential have to use effective contraception, and the situation of -- defect is also advocated.

Second case of contraindication or possible contraindications when the drug generic name has harmful pharmacological effects on pregnancy and/or the fetus/newborn child. In this case the

drug, depending on the nature, the severity, the reversibility of the effect can be contraindicated or it is mentioned that the drug should not be used unless clearly necessary, and the circumstances where the drug could be used should be specified, if possible.

Third situation, no clinical data available but studies in animals have shown reproductive toxicity or are insufficient, because for precautionary reasons we have considered that insufficient data in animals were to be considered as in the same way as positive data.

So in these cases it is stated that the drug should not be used during pregnancy unless clearly necessary with the circumstances to be specified.

The fourth case is when no clinical data are available but animal studies do not indicate harmful effects. The wording is -- proposed wording is caution should be exercised when prescribing to pregnant women.

Situation number five, data on a limited

number of exposed pregnancy indicate no adverse effects of the drug on pregnancy, and animal studies have shown reproductive toxicities are insufficient. Wording is again here caution should be exercised when prescribing to pregnant women.

Sixth situation, situation number six -- data on a limited number of pregnancies are available and indicate no adverse effects, and there is negative animal studies. The sentence is the same, caution should be exercised.

In case number seven, it's where data are available on a large number of exposed pregnancies with no adverse effects seen. In this case, animal data are not even mentioned, and it is simply mentioned that caution should be exercised.

The last case is when well conducted epidemiological studies indicate no adverse effect of generic name on pregnancy on behalf of the fetus/newborn child, and in this case it is stated that the drug can be used during pregnancy.

So that's the actual -- That's the present status of this guideline. Does it mean that what is

yet written is written on the stone? First question. The answer is certainly not.

We can already criticize ourselves or we have been criticized when presenting the data in public meetings. The wording question is certainly a very difficult one, and the wordings we have agreed upon are certainly not satisfactory.

The sentence, caution should be exercised when prescribing to pregnant women, has been found to be very few informative, and should be certainly replaced by something more detailed, because it's not of help for the physician, and the purpose of this section is to help physicians and patients make decisions concerning the treatments.

The same criticism for the sentence, the product should not be used during pregnancy unless clearly necessary -- but I would moderate this criticism, because I think that the circumstances should be detailed whenever possible. But it has been proposed to rephrase it, saying that the drug should not be used during pregnancy unless its use is essential. That's a purpose always received.

The last point: It is clear that there are exceptions to this rule, and that a drug with known effect in pregnant are not always contraindicated, the well known example being the antiepileptic drugs.

Again, we have done only a small part of the job, because we have -- Now it has been decided to complete these general guidance by a more specific one on pregnancy labeling, which has to be drafted. It will be done by all the CPMP working parties, safety working parties, still with preclinical data.

So I am, together with Dr. Klaus Olejniczak from the German BfArM, Federal Institute of Drugs and Medical Devices -- we are be the rapporteur at the CPMP for these guidance, which is -- now it's still the early stage of drafting.

I thank you for your attention.

CHAIRMAN GREENE: Thank you. Are there questions for Dr. Meyer, please?

I have one question for you, please. In your proposed labeling where you state "data on a limited number or a large number," do you use

composite data from multiple studies in arriving at those data on a large number or a small number?

DR. MEYER: Well, the question is yet not addressed, because we've -- the consensus we have yet to say that we should consider limited number. What should be behind these limited number of pregnancies or large number of well conducted epidemiologic studies is one, I think, of the more important tasks we have when drafting the specific note for guidance.

So I cannot yet give you a precise answer on this question. This is to be discussed yet.

CHAIRMAN GREENE: Have all the countries in the European Union agreed to use some uniform system?

DR. MEYER: Well, this guidance is drafted at the CPMP level. So all of the 15 European countries are members of the CPMP, so participated to the discussion and to the drafting of the guidance.

CHAIRMAN GREENE: Dr. Kweder.

DR. KWEDER: Actually, in looking at the annex I do see that you address male mediated effects on pregnancy outcome, and somewhere in here -- I'm

just trying to get a handle on it now -- there's reference to the use of contraception.

Are you putting women of childbearing potential in together with pregnant recommendations -- women of childbearing potential with pregnant women? I'm just a little bit confused.

DR. MEYER: I am not sure that I have --

DR. KWEDER: Are you making recommendations about -- in the pregnancy section about use of these products in women of childbearing potential?

DR. MEYER: No.

DR. KWEDER: Okay.

DR. MEYER: You mean if we are -- do we address the question of the necessity to have a -- to have means of contraception for women when treated by the drug?

DR. KWEDER: Okay. And that would be only if you expected that there were a problem?

DR. MEYER: Yes.

DR. KWEDER: Okay. Just one other question. I don't recall. Do you allow the inclusion

of women in the EU -- What's the policy on inclusion of women of childbearing potential in clinical trials?

DR. MEYER: I mean, the women of childbearing potential are, like everywhere else, excluded from clinical trials, but that's -- I mean, not -- That's not mandatory, I mean, but we do not have more clinical trials with pregnant women that you have.

I think, considering the collection of data, one of the problem we have identified and we are trying to improve is that, even if women of childbearing potential are not included in clinical trials, some participate and there are some pregnancies in the trials, as they are in real life; and it's very difficult to collect the data on these pregnancies, and we would like to improve that a lot.

DR. KWEDER: Okay, thank you.

DR. O'LOUGHLIN: You brought up a point that nobody has brought up today with what Sandi was just talking about, in that if males were to take a certain drug and it was an inadvertent pregnancy, if there would be any problems in the pregnancy due to

the male having taken certain drugs, and if that should be in the labeling at all.

DR. MEYER: You don't think that should be in the labeling? I didn't hear you very well.

DR. O'LOUGHLIN: No. I'm wondering what you're doing. You talk about the male and the female, and using contraceptives. What if the drug was taken and there was an inadvertent pregnancy? I mean, would there be something in the warning about males?

I mean, we've talked a lot about, you know, the female taking the drug, the effects on the fetus, but nothing about males having taken the drugs and an inadvertent pregnancy.

DR. MEYER: Yes. I think -- I mean, on a case by case basis, we will deal with that. Of course, it can be -- It will probably be difficult to give some advise on these points, but I don't think we have to -- we have to take it into account, but that's a general statement for the time being, and we are not as far as to deal with practical cases on this case.

DR. WISNER: We had quite a long debate this morning about how much clinical recommendations

or advice to include in the specific categorization scheme. I wonder how the EU has dealt with that issue.

For example, we talked about would making a statement about monitoring through ultrasounds or perhaps drug serum levels be appropriate. I'm just wondering how your group dealt with that specific issue.

DR. MEYER: There is not yet complete agreement on that. I mean, it was not immediately agreed to include the inadvertent exposure, for instance, in the section, and there are still comments made upon that and some experts saying that there is not a lot to be said in such cases, and that it's very difficult.

Other experts think that there is possibility to advise people to make a survey of the pregnancy and sometimes by ultrasounds, even if there is data only available in animals, because if there is an interspecies specific target organ -- I mean, it's worth doing these ultrasound examinations to check the organ. But it's an area where there is an important

debate still, and I think it will be still debated when we will be drafting the final guideline.

We would like to, of course, to propose that, because as you were so worried about in the States, we know that there are pregnancy terminations when a patient has been exposed inadvertently to a drug which is known to be, for instance, teratogenic in animals, but there is no human data or even there are human data, but there is an alternative possibility which is to monitor the pregnancy to check whether there is or now a harmful effect on the fetus.

One of the most important changes is that in the past a lot of drugs were contraindicated in pregnancy, sometimes because only no human data were available, but as it has been highlighted this morning, when a new drug comes on the markets, no human data is available -- are available.

So it was accepted that this would not be a reason to contraindicate a drug, and that contraindication should be restricted to the drugs for which human data are available with known or suspected harmful effects in humans.

Of course, as usual, we may have some exceptions to this rule, but the idea is not to contraindicate as a excessively precautionary approach all the new drugs because there are no human data available.

CHAIRMAN GREENE: Dr. Kweder.

DR. KWEDER: I just wanted to comment on Dr. Wisner's question. You know, one of the things that struck me about this is that in many respects the EU has a much bigger challenge than we do, because I think they have a number of regulatory agencies who have approached this concept of advice giving or being directive in labels very, very differently.

There are a lot of tightly held philosophic differences among them. So I think he's being understated when he says it's still under discussion.

DR. MEYER: I thought you would encourage me.

DR. KWEDER: No, it's extremely difficult. I mean, we all have -- I mean, I think around the table we have already heard how there are differences

of opinion, and within FDA we have differences of opinion as well, which we struggle with all the time. I think you all have an even greater challenge.

DR. MEYER: Yes, yes. For instance, there was a proposal at sometime to mention in the SPC that for a drug for which there is a suspected teratogenic effect that the pregnancy termination is not the only alternative, for instance, but pregnancy termination is not authorized in all the member states. So it's simply not possible to mention pregnancy termination in the legal text across Europe.

The language question is so important, I think, because when we work together, we work in English, but we have different understanding of what English means, and we -- For instance, we were trying to grade the recommendations, and we discussed a lot to know what was the more restrictive recommendation between "these drugs should not be used during pregnancy" and "this drug is not recommended -- the use of this drug is not recommended during pregnancy," and there were, of course, opposites.

Finally, it was considered being

equivalent, but I would like to know what you think about it. And after that we have the problem to translate that into the different languages, and we have an example where a drug -- it was stated in the original SPC that the drug was not to be used during pregnancy, and the translation in one of the language of the Community -- it was not French -- was it was not to be used to become pregnant. So we have to be careful with that.

CHAIRMAN GREENE: Dr. Wier.

DR. WIER: Francois, very nice presentation. It's very clear in the document the intention of the narrative in Section 4.6, and then going on to the annex, what I like about the annex is it nicely organizes the type of information that's necessary to support the narrative.

Where my compliments stop is why make categories out of this? Why is it necessary to assign numbers of 1 to 8 and to give them this hierarchical representation, because it's at that point where I think the system really fails.

For example, some of the ways that

different types of information are combined and then ranked in combination, such as limited human data with a positive animal finding versus limited human data and a negative animal finding; because the nature of these studies don't always make such combinations possible.

So this is simply my question. Why the compulsion to make categories and to rank them in such a hierarchical order?

DR. MEYER: Well, I think they are not really categories. They should not be considered as categories. They look like categories. They certainly look like, but it's only an attempt to standardize, when possible, the language.

I mean, probably these exact wording or these exact categories will not be followed in most cases. That's not the real point. I mean, we should not -- The idea is that is a background. You start from that, and then you adapt that to the drug.

That should -- But this is only intended to avoid that -- I mean, to avoid that, to have a very different ways of estimating the risk from one drug to

another. So we should try to deal with this system, but -- and after that, we can come with an outcome which is a bit different, but we have to check were we right to behave differently, and sometimes when checking that, you have to say, okay, I've contraindicated this drug, despite the fact that there is no known toxicity in humans.

We've done that recently. We've done that recently for ribavirin. It's contraindicated in pregnancy, and there is no data available in humans. So that's -- but it should be an exception or maybe, if there are several exceptions, another so called category should be created. But in another example, if we contraindicate a drug because it's only there are no human data available and possible animal toxicity, in many cases it would not be acceptable.

So that's just to remind the general rules, but we should not consider that as fixed categories, and it's not written in stone. Even, you know, the wording, we have to think again to improve it, because it's not satisfactory yet.

CHAIRMAN GREENE: Thank you -- One more

question? Yes?

DR. DeGEORGE: I just wanted to ask a question. It seemed to me that, in looking at the way you were evaluating the data, that you were pooling together all outcomes in your animal studies, regardless, other than fertility, that any outcome is actually pooled to come to your recommendation. You're not giving any sort of specific recommendations based on any specific outcomes in, say, any of the endpoints that one might measure.

DR. MEYER: I don't think it should be really pooled there. I mean, if there are outcomes which have to be separated, they should be separated. I mean, it's only for the purpose of clarity of the presentation and of the length of the document, but in most cases it should be specific to the outcome, certainly.

DR. DeGEORGE: Thank you.

CHAIRMAN GREENE: Thank you very much.

Dr. Kweder, with your permission, maybe we'll take a break now and then we'll entertain the questions. We'll return at ten minutes of three.

DR. KWEDER: You don't need my permission.

(Whereupon, the foregoing matter went off the record at 2:35 p.m. and went back on the record at 2:53 p.m.)

CHAIRMAN GREENE: We are ready to reconvene, please. I think we're ready for Dr. Kweder to present the questions that we are to discuss.

DR. KWEDER: I think that I'll spare you reading them in great detail, but I want to start with just remind you what my helpful hints were.

First, if this seems difficult, it's because it is. That is why you're here. It's why it's taken us as long as it has to go from a Part 15 hearing to this meeting.

What we seek from you is general guidance. You don't have to give us specific recommendations about which everyone at the table agree. We recognize that there is going to be some variability in opinion, and we'll take that under advisement.

If you can develop some consensus, it's helpful, but it's not a requirement. What is helpful is, if you don't have consensus, if we could

understand why and where the disparity comes from, that's always useful to us.

Again, to remind you, it's going to be our responsibility to write a new regulation. It's not yours. You don't have to come up with, you know, a specific system or a matrix. That's probably above and beyond the call of duty at this point in time.

So in terms of the questions that we have, I would just like to remind you we only gave a brief presentation this morning of the preclinical things that are happening in terms of the actual evaluation of data.

We have a separate process that's ongoing to evaluate that, and it is something that ultimately this committee may be called upon to comment on in the future, but that's not the topic for today's meeting.

The questions that you have before you, we limited ourselves to one page.

CHAIRMAN GREENE: Can I ask one question before you start -- launch into the questions.

A question was asked, does the FDA at this point have a time frame or a timeline in mind for

completing this deliberation process, implementing, let's say, a new set of regulations, and getting the new whatever we decide in terms of labeling deployed?

DR. KWEDER: I think that the answer to that question depends greatly on what your responses to the questions today are. If we get the sense that we're going in the right direction, I think that it will be sooner rather than later.

If we hear from you that, boy, you folks have this all wrong and you need to complete regroup, we're talking about a much longer period of time.

What we could -- I guess it would probably be fair to say that within the next few months we would like to put something out in the Federal Register.

What we actually envision is we envision a regulation that's actually on the simple side with a guidance document -- remember, I explained the difference this morning -- that's a little more -- that goes into a little bit more detail but is not quite as binding as a regulation.

So that if we find that things aren't

going well with how we're implementing this regulation, we have some flexibility to change. One of the problems we have with the current regulation is that it is quite detailed, and it almost boxes us in more than is helpful.

So the answer -- The short answer is it depends on what your comments are today. Our goal is to get a proposed rule out within the next few months.

CHAIRMAN GREENE: So in a best case scenario, today everybody just throws roses and no brickbats?

DR. KWEDER: Oh, yeah.

CHAIRMAN GREENE: You're talking about having something in the Federal Register by September?

DR. KWEDER: Where is my -- Joe? Ginny? Those are the lawyers.

CHAIRMAN GREENE: By the end of the calendar year?

DR. KWEDER: I think by the end of the calendar year. My goal is sooner than that, but I think that's probably --

CHAIRMAN GREENE: And then you said

there's a 60 day comment period?

DR. KWEDER: -- comment period, and then we decided, based on those comments, how much we need to alter the proposal, if at all.

CHAIRMAN GREENE: Then if there are no major alterations, you folks at the FDA roll up your sleeves and get started? How long is this going to take?

DR. KWEDER: And we just put it out as a final rule. We put it out as a final rule, effective immediately, usually with an implementation plan. One of the reasons that we brought this before a committee such as yourselves is because we'd like to feel confident that, when we put out a proposed rule, it's pretty close to what the final regulation is going to look like and, hopefully, that saves us time. That's the idea.

CHAIRMAN GREENE: Thank you.

DR. KWEDER: So any other questions for me? I'm not going to read the specific questions other than to just hit a couple of the key words.

Under the format and content area, t he

kinds of things that we're asking are about usefulness of the format and content we've generally proposed. We would like you to get back to the issue of how specific and detailed recommendations should be, how to address risk in the appropriate context for different readers, and give us some guidance on relative merit of describing risk quantitatively and qualitatively and, in particular, what kind of terms are you thinking when you answer that question.

We do have a question about how we should select information for the discussion of data section. We have three questions regarding risk communication. In particular, where we don't know very much, how should we communicate this lack of information, and how can uncertainty associated with the predictive value of some of the animal reproductive studies, particularly in the absence of human data, best be communicated?

Finally, there is a question, because we have had many comments on this made to us, about risk language or descriptive language that has acquired what was probably unintended connotations that should

be avoided in providing advice or in describing risks.

If you can give us examples of what that might be and suggestions for alternatives, that would be very helpful.

So I'll leave you to --

CHAIRMAN GREENE: Can I suggest that we take them one at a time then, although --

DR. KWEDER: You can do that, however you like. You can do them in order. You could do them in reverse order. You can randomly select.

CHAIRMAN GREENE: Well, I'm just concerned that we'll get a little bit too unfocused and chaotic if we don't address the questions one at a time. So why don't we start with the first question then, and I'll solicit comments from the panel or questions for any of the FDA staff with regard to question number 1, the utility of the proposed reorganization.

What I would say is that, although there is consensus that the current categorization is not useful and, in fact, sometimes misleading, I do think that we need some relatively shorthand way of communicating what is a large quantity of complex data

in many cases, so that simply heaping several pages of data on a physician's desk is not going to be helpful, and there does need to be some relatively brief summary, almost, as some of the physicians said in the focus group, headline format, if you will.

There does need to be some relatively brief summary that a physician who is busy in his or her office seeing patients doesn't have a day or two to research an issue, can refer to relatively quickly.

I think this would fulfill that need. Dr. Briggs.

DR. BRIGGS: I would certainly second that. I did sort of a mini-poll before I came here from physicians on our medical staff, and of the ten or so I talked to, probably seven of them -- the first words out were keep it simple.

In my experience, physicians -- These are obstetricians I'm talking about. They probably know nine or ten drugs extremely well, and that's the ones they use day in and day out, and they know the problems of those drugs and whether they can be used in pregnancy, what they are, what part of pregnancy.

It's when they get beyond those drugs, that's when they get in trouble. So they're pretty sharp, and they call someone to get the information. I have physicians that won't even buy my book there, because they know they can call me for a nickel and get free information, which is all right. They're good friends, but that's the type of situation they're in.

CHAIRMAN GREENE: Dr. Andrews.

DR. ANDREWS: I agree as well that we need to come up with a very brief summary that says what we know. I'm concerned about the clinical management section, and most concerned that we may be giving advice on pregnancy medicine, going beyond what we know.

So I would advise us to steer clear of clinical management. I think that it's too easy to predict, to attempt to predict based on animal data, when we really don't know, and the Roselens example is a good one of trying to project human experience from animal studies.

Likewise, I'm concerned that we might

conclude there is no risk based on 100 human exposures when we can't do that. That's really going beyond the data.

So I would advise us to have a section on a summary of the risk assessment and perhaps clinical considerations where we can reasonably draw some inferences relating to clinical practice based on solid data, but I think I would steer clear of prescribing medical practice.

CHAIRMAN GREENE: Can I push you a little further to clarify that? Do you feel that there shouldn't be any recommendations with respect to clinical management or that the bar should be set fairly high, that the clinical management suggestions should only be made when they're clearly supported by data?

DR. ANDREWS: I think the bar should be set very high. I would be very nervous about having three categories that must always be completed. I think that that would lead to endless and fruitless discussions that would offer really no help and a false sense of security.

I think we've heard data today that suggests that, if we give a top line bit of advice, that's all the clinician might read, if they read the label at all, and I would much rather have the person dig down and see what the data really are or turn to experts or other references.

As we've been saying, I think probably the most useful part of this large green volume that we received was the comparison for individual drugs at the label and the different summaries of the data showing that very expert and thoughtful individuals can summarize the data and draw different conclusions.

I would much rather see that being done in the context of a patient/physician relationship than a manufacturer coming up with proposals or having something set in stone.

CHAIRMAN GREENE: Okay. So you're not categorically opposed to recommendations for management, as long as it's based on solid data?

DR. ANDREWS: Very solid data.

CHAIRMAN GREENE: And I think the fact that different acknowledged experts could reasonably

differ was brought out quite well by Dr. Meyer's data on various countries in the EU where the same compound was either recommended for liberal use or contraindicated, and everything in between.

Yes, please, Pat first.

DR. WIER: I am hearing that some people will feel that physicians won't read the discussion of data, because it's just too many details. I know that there will be other people who find it insufficient in the level of detail, the people who really want to drill down.

So it causes me to raise the question, is it necessary that the discussion of data, which I think is important -- but is it necessary that it appear in the package insert, and why can't we take advantages of other media to allow people to tap into the discussion of data?

It's important that we have it. It's important that the evidence supporting the summary statements be available to people, but I'm questioning can it fit? Is it practical? Is it the best thing to do to put it in the package insert as opposed to

making it available on a Website, for example?

CHAIRMAN GREENE: Jim.

DR. LEMONS: I tend to agree with the final two comments, but because everything that's going to be in here is based upon the data. So I would once again ask for some systematic way for the reviewers to objectively identify or articulate the quality of the data.

Again, that can be done in human studies. I don't know if this can be done by January, because -- and I'm not sure what the timeline is for the preclinical review group to come up with something that can give us a guidance on how to interpret animal data. This is still a real enigma.

Regarding clinical management, I think it may be okay, it may not be okay. It's okay if it's truly based on what we would consider quality evidence. I mean, you can say monitor this, this or this, if it truly is supported by large epidemiologic or controlled trials that provide substantive human data. But shy of that, I think it's going to be difficult and risky and, as the time changes, it is an

important issue whether clinical management can be posed in a timely fashion.

That may be better left to the specific organizations such as ACOG or the AP regarding specific uses of data. To me, that's going to be the essential ingredient in developing a sound proposal for risk.

Again, risk is probability. Hazard is, I guess, the actual identified adverse event. So those are the two pieces.

CHAIRMAN GREENE: In that regard, the FDA doesn't necessarily need to reinvent a wheel that they might be able to borrow, for example, from the AHCPR, the Agency for Health Care Policy and Research, which does categorize studies on the basis of the quality of the evidence in the study. So that wheel would not need to be reinvented.

Yes, Ms. Scott.

MS. SCOTT: I am Julia Scott. I'm the consumer rep on the board.

It was good for me to sit through this morning and really be reminded of the concerns of

clinicians, because I basically come from the point of view of consumers and individual women, and this is an area that is long overdue, and I want to congratulate the FDA for kind of biting the bullet on this also.

As a consumer, I think it's going to be very, very important for whatever we come up with, for it to be in language that is understood by -- I don't want to say everyday people as opposed to the medical jargon.

This is a very complex issue. We can't make it simple overnight. So I get a little concerned when I hear about just having, you know, a simple little boxes, little straightforward paragraphs on this, partly because much of this is in the dialogue between the practitioner and the woman.

So trying to err on the side of providing enough information for both women and practitioners is going to be very, very difficult. So anything that we come up with as a result of this meeting, there's going to have to be some back-up by some other organizations about training of practitioners or getting this information to practitioners.

I think women generally -- they want full information. They don't want things kept from them because somebody else has determined that they either can't understand it or it might frighten them. I think, as part of the medical community, we have to be clear about what it is that we don't know.

Part of this deals with the high expectations that women have when they sit with their health care provider. We've been trained to think that the provider knows all the information, and we're now starting to acknowledge that we don't know it all and that this would be a shared thing that we are going to walk through together.

I think, if women feel that they're getting full information, that some of the information is scary, but there is --if the practitioner can share from their own experience and translate the data in terms of the real implications for that individual woman, as far as we know, that that goes a long way toward getting us to where we need to be in making these very difficult decisions.

Also, I'd like to have the FDA really

think seriously about having some kind of registry. We are a long way from doing actual clinical studies on pregnant women, and there are ethical issues.

There are safety issues, a whole bunch of issues; but it seems to me, from what I heard in this room this morning, at least for a great many of the practitioners, you've been using some of these meds with pregnant women for a long time, and there should be some way we should be able to capture some of this information so that, while it may not point to one drug actually -- a causal relationship between a fetal defect or a maternal problem later on, it could possibly be a flag.

It could show perhaps that there is -- something seems to be going on around here with this particular medication. So I would really like to encourage, whatever comes out of here, that we look at some of the registries that some of the drug companies have used and other models, and see if we could move toward some kind of national registry so that we could keep track of these women and their offspring to highlight problems.

I apologize for taking so long, but I have an appointment. I have to leave. I'm very sorry for that. So I wanted to try to get the consumer rep perspective in there.

CHAIRMAN GREENE: Thank you. Other comments. Yes, please.

DR. TAYLOR: Alan Taylor from Gilead Sciences.

I think on balance that the FDA proposal is quite good. I believe that having a clinical management statement that's fairly closely tied to the summary risk assessment will allow us to give some advice to those physicians who don't feel competent to make those kinds of decisions.

I wouldn't want us to be highly prescriptive in that, but any advice which a reasonable group of experts would agree upon, I think, is something that would be helpful to physicians.

I think that it's a good idea to include the preclinical information for those who feel strongly that they would like their own assessment of the information. So I would sort of oppose removing

that information.

We've spent a lot of time talking about presentation of information and how various communities and individuals will look at information in different ways. I think it's really important for the information to be there for people to make up their own minds.

Additionally, I am hopeful that the agency will provide some standard templates for how that language will be provided in the package insert. I think it's really quite important in improving the understanding of that information and ensuring consistency of interpretation of data. It also removes potentials for commercial advantage from one group to another.

Overall, I think it's a good proposal.

DR. O'LOUGHLIN: Not being a physician, I really don't understand the whole concept behind clinical management per se, but the one thing that I do understand is risk management. I think I just wanted to add to Alan's comments in that, if there are risks associated, that you probably want to have some

management plan for those risks at a high level.

I agree with the woman at the end of the table that I don't think you want to get to all those details of step one, two, three and four and march down that way, but you want to give some kind of guidance, and I think it would be very helpful to the patient, too, to understand that guidance and what risk it's associated with.

CHAIRMAN GREENE: Dr. Hammond and then Dr. Jones.

DR. HAMMOND: Along those same lines, I think it is important, if we know and are using information about using drugs in certain trimesters, that it be established clinical practice to give, not give, or give in the first trimester, that that information needs to be included in the clinical assessment; because for people who are not obstetrician/gynecologists, that's information they may not have available. And that is specific.

DR. JONES: I have two unrelated issues, and one relates to your question, I think, do we need -- how much of this review of the data do we actually

need here?

I'm not sure exactly how much we do need, but it seems to me we need a significant amount to back up the other two parts of this thing. I don't know where you stop and where you start, but I think that we do need a significant amount.

The other issue that I would like to bring up is whether, in fact, we need as part of this, this fertility section. I, for one, do not believe that we need the fertility section as part of this.

I think it's appropriate -- I think fertility is a very different issue than pregnancy and lactation, and I think that the fertility aspects can go through other parts of the broad statement. I don't think they should go here.

CHAIRMAN GREENE: There have been several allusions to expert opinions, and I'll just point out that in the AHCPR ranking, expert opinions are the lowest level of recommendation. The definition, of course, as everyone knows, is an expert is someone from out of town with slides.

DR. JONES: Well, I'm not even that.

CHAIRMAN GREENE: Yes, please?

DR. WISNER: I would like to comment specifically on the discussion of data, the subheadings that were proposed.

The first was embryo-fetal death, which I think is self-explanatory, and the next one was dysmorphogenesis or structural alterations. The third is growth retardation, which again make sense, but I would also add growth enhancement, which is a teratogenic effect of some agents.

The fourth is functional toxicities, which I took to mean developmental or, to some extent, neurodevelopmental toxicities. So I was not quite clear about that particular topic.

The fifth that I think is missing is neonatal toxicities or toxicity that occurs in the newborn due to exposure to a drug immediately prepartum.

Then there was maternal toxicity. Again, I was not clear about what exactly that meant. I thought it might mean toxicities that were specific to the Mom because the drug interacted in some way with

the pregnant state.

Then the final one, labor and delivery -- again, I wasn't quite clear whether that referred to drugs used in labor and delivery or drugs that might be used during pregnancy that could impact labor and delivery.

So I think some clarification of those specific topics is important.

The other is Mary's comment about the developmental specificity where some of these categories are only relevant for certain phases in pregnancy.

Finally, I was somewhat troubled by what I perceive to be a very negative slant; for example, growth retardation and not enhancement and other kinds of toxicities when there are certain agents that are used in pregnancy for specific outcomes perceived as advantages, like for example, drugs that might be used to make pulmonary development more rapid prior to a birth.

So again, I think that slant is toward the negative, and I would like to see that broadened.

CHAIRMAN GREENE: Dr. Kweder, would you or your staff clarify some of the aspects of developmental toxicity that were just asked about, or do you need time to think about that?

DR. DeGEORGE: Sandi is sure I can do this. In the functional toxicity, we were really specifically speaking about developmental abnormalities. Primarily the ones you do see are the ones that are neural, behavioral effects.

That really is the standard endpoint we can get, but clearly there are other functional -- As Dr. Morse mentioned, there are other one, reproductive competency, for example, something that may be impacted by early exposure.

Actually, I was trying to find where we said something about maternal toxicity. I think that what we were really -- and I haven't been able to locate that. So I'm not exactly sure where that comes from, but in the examples when we talk about maternal toxicity in the animal data, we're really trying to focus on whether or not a finding is occurring in the presence of maternal toxicity which may confound the

interpretation, not as to whether it's maternally toxic per se.

That may be the wrong answer, but I think it's the right answer, but I don't think we had a section called maternal toxicity, but maybe we did.

DR. KWEDER: I think I can address this as well. I agree with you. This -- I'm glad you picked up on this, because I made the distinction in my talk, and I think it comes out in the proposal. It's an area we need to work on.

As a clinician, I think that we need to separate out maternal toxicity in animal studies that leads to observable effects in offspring, compared to toxicities in the clinical setting that may be magnified or otherwise affected by pregnancy itself.

I think an example is that there is some literature -- The example I most commonly cite is that there is some literature that at least suggests -- level of evidence, I'm not sure -- that INH hepatotoxicity may be more problematic during pregnancy than in non-pregnant women.

Similarly for some of the -- not a

toxicity -- is idovudine. The original descriptions of fatty liver were in pregnant women. So those kinds of things probably, if we do have data, even though we don't necessarily do controlled studies, though some people might and there are some in the literature -- we should somehow find a way to address those as well, because for the clinician and patient those are just as important.

CHAIRMAN GREENE: I think there is ample evidence in the literature from exposures to a number of drugs that the liver is uniquely susceptible to toxic influences during pregnancy, for reasons that aren't yet understood, going back to tetracycline in the 1950s.

DR. KWEDER: Right, exactly.

CHAIRMAN GREENE: So I think that's quite clear, that the liver is particularly sensitive.

I would also assume that one of the developmental "toxicities," quote, unquote, that you're referring to are problems with adaptation to the transition to neonatal life. Would that not be true, things like hypothermia, hypoglycemia, and such?

DR. DeGEORGE: They may be more direct toxicities, not -- If you're talking about transient effects, I think we would consider those more direct effects on the neonate.

You have to keep in mind that, when we're talking about animal studies, the timing of birth and the age, the developmental age, of the animal is actually different than the developmental age in humans at birth.

So there are some confounding factors in extrapolating the various findings.

DR. KWEDER: But we would include -- If we had human data on those effects, that's probably where we would include it.

DR. MITCHELL: Mike, may I interject?

CHAIRMAN GREENE: Oh, yes, please, Allen.

DR. MITCHELL: Or should I just get in the queue? I can't tell how many hands are up.

CHAIRMAN GREENE: No, you're it.

DR. MITCHELL: Oh, okay. I have a number of thoughts and comments. One is that I think there needs to be some clarification whether the proposed