based on gender, based on age, based on cultural background.

I think that just adds another level of complexity about how to present it, and I think it gets to the point that a lot of people are beginning to believe that, again, you have to use multiple approaches in order to really interact with the patient in a way that's meaningful for them.

I think that's the biggest challenge. I'd love to hear what sort of experiences you've had with genetic counseling, because I think that's the next great frontier and, to be honest with you, as a general internist that's the next frontier for us, because we're going to start to be doing a lot of genetic testing within the next decade, even in a general medicine practice with regard to things like the breast cancer genes and others.

You know, the genes for colon cancer aren't far off. What we may be actually extending, instead of a fecal occult blood test for stool, sending patients off to get a gene test of their stool. It's really come down to that. Believe it or

not, it's around the corner.

So I'm sorry I don't have more information, but only to agree with your observations.

DR. ROSENE-MONTELLA: Karen Rosene-Montella. I actually have a comment on an answer to that question, because I end up doing this a lot, based on what I do.

One of the things I always have to say to someone and ask a patient is what are you going to do with this information? Are you making this decision alone? Are you making this decision with your mother, your father, your partner? Who else is going to be involved in the decision that you're going to make, because you're quite right that they may view it one way and someone else may view it another.

In fact, you may be dealing with someone whose decision making is based on what someone other than you think as well. So I always ask that question as well, and then pull in whoever that is so that there can be a full discussion about it; because otherwise, you really don't know what someone is going to do with the information that you've given them.

DR. HOLMBOE: I think that's a great point, and I'm sorry I didn't mention that. But we see that sometimes in men, even with prostate cancer when I talk to them, that many times what's driving their decision is actually their spouse, you know, and it's often the spouse's fear of them dying of cancer.

So the spouse is far more willing to put up with impotence and incontinence than perhaps the patient is. So I think that's a really important point, and you can imagine in pregnancy where now you've got two people involved in the outcome of the trial. That becomes a huge issue.

DR. KWEDER: Sandra Kweder from FDA. I just wanted to comment on Eric's point about perceptions. One of the comments -- Some of the discussion we had at the Part 15 hearing related to the fact that most patients who enter pregnancy assume that pregnancy itself is a risk free endeavor.

We were actually encouraged to keep that in mind in how we address a new labeling format, that perhaps in some situations there is a role for stating up front, you know, that the risk of neural tube

defects or abnormalities or preterm labor, if that's what you think the potential effect of a potential product is, is X in general; and compared to that, this is what we think about this product.

It takes on a very different meaning, and I think that some of what Dr. Koren would have probably touched on, were he here; because most people think that, you know, the thing that happens is you get pregnant, you're pregnant for 40 weeks, you have an uncomplicated delivery, and you go home with a perfect baby.

We all know that that's not necessarily the case, that there are population risks that most people don't have in their general frame of reference or, even if they do, they would prefer not to think about. When you frame other potential risks in that context, it often helps them.

CHAIRMAN GREENE: Yes, please?

DR. WISNER: Kathy Wisner from Case Western Reserve. I think the talk was wonderful, and it made me think that what we really do is use our expertise to transmit information to patients so that

they can use what I think we have to recognize is their expertise at valuing all those components and making an optimal decision for themselves.

In psychiatry, which is the field in which I work, I have patients who have cognitive dysfunction by virtue of their disorder, and transmitting that information is difficult. So in my clinical practice what I always do is ask the patient to summarize for me what they heard from my discussion, and sometimes I'm floored.

I might give what I think is a brilliant discussion, and the take-away message from the mother might be you're telling me my baby is going to have a defect. Then I have to process through that information so that I hopefully can get to a more realistic understanding on their behalf, so they can use the information.

DR. HOLMBOE: I think the other point I would make is that we shouldn't see risk discussion as a one-time event. I think that's something else that often happens, that we think if we provide this information once -- I think informed consent is a

perfect example -- that somehow the patients are going to get it.

This stuff can be very complex. It's hard for physicians to understand, and I think the other thing to consider that you bring up is kind of a sequential process where you let them kind of process it, bring it back, readdress it, and find out where the lesions may be.

You know, again it's very hard for people to process, particularly quantitative information that we as physicians have trouble using effectively. I can imagine that a number of patients have trouble processing that.

DR. CHONG: Cynthia Chong from Albert Einstein. I want just to add to the complexity of relaying risk to patients. At this point we also have patients who have access to electronic media, and this is usually in the format of not surfing the Web, but the pharmacists usually hand out these little stickers with each medication that they come, and they're very complex, often ten to 20 pages.

So the discussion of risk often does not

begin with your conversation with the patient, but their availability of data in a format. So, therefore, the task of this committee to be able to relay this to patients has become complex in yet another fashion.

DR. HOLMBOE: And I think you speak to the availability bias, if we do talk about the Internet. I'm sure everybody has had this experience where you get a patient who calls in and says, listen, I just read this drug insert my pharmacist gave me, and I don't want to take this medication. They read the 403 things listed on the insert, you know, with a one percent or less chance, and they just don't want to take it. So it's a very important point.

CHAIRMAN GREENE: Jim?

DR. LEMONS: That was a very nice presentation. Actually, all three were --

CHAIRMAN GREENE: Jim, please identify yourself.

DR. LEMONS: Oh, I'm sorry, Jim Lemons from Indiana. All three were very nice, and I know you and Sandra both touched on the other aspect, I

guess, and that is the risk of not potentially undergoing a beneficial treatment or really balancing the benefit.

I mean, there are many examples. You gave one about the relative risk reduction of stroke, which relatively might be 50 percent, but absolute reduction might be less than a tenth of a percent. In the perception of an 80-year-old man versus an adolescent who has mild hypertension, obviously, the adolescent will never die, and the 80-year-old man may see his days coming to an end.

Similarly, HIV during pregnancy -- I wondered if you could comment on how one couches informed consent, for example, for a woman with HIV who can successfully minimalize the risk to her fetus and somewhat decrease the -- but there may be unknown risks, obviously, to the newer treatments that are coming along.

DR. HOLMBOE: I think here you're dealing with a large degree of uncertainty. You, fortunately, do have some data that shows that treatment does reduce the risk of transmission, and I think that's a

powerful message to give to somebody like that, particularly in something that carries a fair high dread, you know, potential.

I mean, we think back to Slovic. You know, that's something that is catastrophic, you know, for a fetus to have HIV. We also know that kids don't tend to do very well with this particular illness.

So I think that's one thing that can be very helpful in the sense you can use the bias sometimes of some of these perception difficulties or natural biases we have sometimes to your advantage, if you really feel it's in the patient's best interest.

I think that, you know, many times you just have to be honest, up front about it. We really don't know what this means ten to 15 years. We just don't have the data.

What I find is that many patients are willing to accept that, as long as you're honest with them. It may make them uncomfortable, but you know, patients also aren't stupid. They realize that, if a new therapy comes along, it also comes -- Even if it's been approved by the FDA, etcetera, they know there's

a certain degree of uncertainty associated with taking a new particular medication.

I think, as long as that's acknowledged up front, then everybody -- You know, it's kind of acknowledging the elephant in the room, so to speak. Everybody understands that, yes, there are some potential long term risks here. We need to acknowledge that, but here's what we know today.

We know the potential benefit for your fetus, and so based on that let's make the best decision for you and your fetus with regards to HIV.

DR. KWEDER: Sandra Kweder, FDA. I'd like to just turn that into a question for the committee to think about for your later discussion, which is: How -- Do you have suggestions in labels for how we deal with the uncertainty factor? How do we -- Do we just come out and say we're uncertain, and how do we say that, and when?

I think it's clearly an important issue in the patient/physician dynamic, and remember that what we're doing in labels is we're writing it for patients -- for physicians, who will then have to talk to

patients, keeping in mind that patients will read it as well.

CHAIRMAN GREENE: Dr. Holmboe, before I allow you to leave the podium, I'd just like to give Allen Mitchell a chance to ask any questions, if he has them. Allen?

DR. MITCHELL: No, I found the presentation fascinating, but I don't have any questions at this point. I do have one for Sandi Kweder, and I don't know if she's at the rostrum or this is the time to ask.

CHAIRMAN GREENE: Okay. Why don't I let Dr. Holmboe sit down then, and find -- Allen, why don't you go ahead with the first question for Dr. Kweder then, please.

DR. MITCHELL: Thank you. Sandi, you stated very clearly that the categorical -- the letter designations were required by law. Where does that leave FDA and the Advisory Committee in terms of -- Well, I think on one of the slides the proposal was not to revise but to change the information.

Are the letters still going to have to be

carried with various subsections or are you saying that there's a proposal to actually change the law? Am I missing something?

DR. KWEDER: No, you're not missing something at all, Allen. It's actually a very good question. That is why I said that -- I specifically said that the categories are there by regulation and law, which means that we can't just decide today that we don't like them, so we're not going to apply them. We must.

What we're trying to do is we are -- Our goal is to develop a new system that we would then put out as a law that would replace that. Remove the requirement to have these, and replace it.

You know, there will be, certainly, challenges to implementation of that, and there is sort of our problem; because it would be very resource intense to say "and starting next January," to pick a date out of the air, "all products that are on the market now, you know, all 1600 of them, must go to this new system."

Well, that would just be -- That would be

an impossible thing to achieve. So what we would likely do is put forth -- put out a new regulation, a new rule, and with an implementation plan. You know, over X period of years we'll evolve products to comply with this new system.

Does that answer your question?

DR. MITCHELL: Yes. So in other words, FDA would come up with an alternative, and then hope to get Congressional approval for it? Is that a way of stating it?

DR. KWEDER: In this case, it's not Congressional approval, which is probably a good thing. What happens is we put forward a proposed model or a new rule, and we publish it in the Federal Register. It goes out as what's called a proposed rule. This is the system that exists.

We must publish it in the Federal Register, and take public comment for some period of time. It's usually 60 days after that. The public has a chance to offer their comment, pros and con, what they think of this, and then what we do is we take that comment and we make a decision, are we going

to go forward with this, is it a rule or are we going to revise it, and we subsequently publish a final rule.

DR. MITCHELL: So then the -- I'm confused, and maybe it's not relevant. But the Congressional mandate then, I gather, didn't specify the A,C,D,X.

DR. KWEDER: No, that's a regulation.

DR. MITCHELL: Okay. So it's within FDA's authority to revise the regulation?

DR. KWEDER: We do have -- Right. Yes.

DR. MITCHELL: Fine, thank you.

CHAIRMAN GREENE: Let me -- Mike Greene -- ask you another question or make a recommendation, if I might.

In response to your question a minute ago about how do we handle the uncertainty, may I suggest that in whatever future labeling we come up with, that we resolve how to deal with zero numerators.

Several years ago Dr. Abbie Lippman-Hand published a paper entitled something like "If Nothing Went Wrong, Is Everything All Right?" where she dealt

with the problem of zero numerators.

I would just like to make a plea or a pitch that, whenever a zero numerator type of study is reported, that a 95 percent confidence interval of the upper maximum bound of risk for that finding is included so that it isn't conveyed as a zero risk.

DR. KWEDER: Actually, I'm glad you made that point. We make that to our reviewers in our reviewer's guidance document, that just as they should view, say, a case series of ten with positive findings as being -- take great care in interpreting what that means, they should be similarly careful in a case series of zero, with zero findings.

CHAIRMAN GREENE: I'd like to ask one other question of Dr. Morse as well as Dr. Kweder possibly.

Dr. Morse touched upon the issue of how to extrapolate animal data to humans, and he touched on the issue of what I've always been taught, is what we call dose ratio, the notion of the ratio of the dose that's required to produce, let's say, teratogenic results versus, let's say, death of the fetuses or

even death of the mothers.

The devil is always in the details here. When you have a situation where, for example, a teratogenic or other unwanted adverse effect is only seen in the presence of a dose that is lethal, let's say, to half of the fetuses or lethal even to half of the mothers, how is that kind of information going to be interpreted for patients, since that is usually many, many times, sometimes orders of magnitude, greater than the maximum dose intended for human use?

Is there going to be some formula for how that information will be interpreted for humans?

DR. MORSE: Actually, you've raised several points.

CHAIRMAN GREENE: I'm not sure your mike is on.

DR. MORSE: You've raised several points about the integration tool, actually. To address the question of, let's say, a positive effect being seen only at clearly maternally toxic doses, there's actually, as part of the factor that deals with the characterization of the response in the F-0

generation, a weighting that takes into account whether or not that adverse outcome of the offspring was seen only under circumstances when there was clearly a demonstrable adverse outcome in the parent generation, the assumption being that one could -- the outcome, the adverse outcome in the offspring be a result of or carry-through of the adverse event seen in the parent generation and, therefore, would not be weighted as significantly as something which was seen in a circumstance in which there was no demonstration of adverse outcome in the parent generation.

There's also in one of the end factors of the integration tool the actual dose, the relative doses, used in the animal studies and the human studies, and the thresholds have been set for that one particular category very specifically, that multiplicities of ten or less increase the perception of perceived risk. Those between ten and 20 have no impact on the perception of risk and, if multiplicity is greater than ten and twentyfold for the animal effect being demonstrated versus the human exposure, then there is a perception of a decreased risk for the

human condition.

CHAIRMAN GREENE: Yes, please, Jim.

DR. LEMONS: Jim Lemons from Indiana. Just a related question for either you or Sandra, and it's, I guess, germane to both the human and the animal studies. That is, in the human studies there are, I guess, more well documented, systematic ways to evaluate the quality of the evidence which have, you know, in recent years been promulgated.

I guess, is there a plan to incorporate some systematic method to report the quality of the evidence? I don't know how simply that can be done, both for the animal studies and for the human data which may or may not be available?

DR. MORSE: There are certain standards that all products undergo as they are being developed, and toxicology studies are typically carried out under what's called good clinical practice, good GLP conditions.

So there are certain minimum standards that must be met in any toxicology study in order to be acceptable for review by the agency. I'm not quite

sure what you mean in terms of communication of that in the product label.

DR. LEMONS: I was thinking more in terms of in rank order for the human data. If we have a large randomized clinical trial powered to answer the hypothesis posed, then that probably is the first order of rank. If you get numerous, you know, such trials that can be analyzed together, that poses a more powerful case potentially, and that's higher order rank than cohort historical studies and case reports, as Sandra had said, etcetera.

DR. KWEDER: I think I can address this a little bit for the human studies. This is something that we have certainly struggled with.

If you look historically at the way we've approached labeling in this area, we have been in a situation many times where we've had data in the area of clinical data related to pregnancy where we've had data submitted to us, large -- potentially large bodies of data, but we've felt that the quality of the data was such that we couldn't say anything meaningful about it, and so we've just said -- We've not said

anything about it.

We did get some feedback on this at the Part 15 hearing, that by not addressing those things, particularly if they're out in the medical literature, even if you don't think that they tell very much, it creates a credibility gap.

I mean, we'd like to hear from you. Well, how can we deal with that? I think one example of a group that does this is the TERIS group. You have some examples of the TERIS narratives about risk in pregnancy in your packet, and they say right up front here's how much data there is, here's its quality.

You know, so all the stuff we've just said is -- these are the caveats. You know, we may think this, but we acknowledge that the data are not very good quality or they're of excellent quality or that sort of thing. Is that the sort of thing we ought to be doing in product labels?

Actually, I think Joe DeGeorge has a follow-up from Dave Morse.

DR. DeGEORGE: I wanted to comment a little bit about the issue of quality. Joseph

DeGeorge.

What we have in the tool is a mechanism that looks at -- from the animal data, is basically a mechanism of looking at multiple sets of animal data and trying -- The more reinforcing they are of each other, the better we believe the quality of the findings. So that's built into the tool itself.

I think that addresses, as Dave pointed out, good laboratory practices. Almost all studies are conducted according to a certain standard with certain numbers of animals and certain specific designs.

There are cases where we think that the quality of the data may not be adequate. As Dave pointed out, maybe the model is not the right model, is not appropriate either in the fact that it gives a positive signal or the fact that it gives a negative signal, and within our approach we say that we would maybe describe the study but actually also describe the inadequacy of the study in answering the question.

DR. MORSE: Actually, if I could add just one more thing. You made a comment about historical

databases and cohorts. There's actually normally in any given animal toxicology study a concurrent control group which is included in the study, and historical databases are really geared more to assessing the quality of the study as does the control group fit into the historical expectations for any given abnormality.

If you know that it's outside of that range, then you begin to question the quality of the study that you're looking at. At the same time, there are some instances in which the historical databases serves the function of giving you a range as to low incidence events, because the toxicology studies are generally relatively small in the number of animals that are included, and for events that occur at fractions of one percent of the time, the ability to detect them statistically is not really feasible within those designs.

So you need to have some framework of reference as to what the incidence of these low events are in a kind of cross-study perspective; in other words, the control groups from many, many studies

conducted over a long period of time so that you can try and tease out issues of low incidence rates for unusual findings.

DR. WIER: Patrick Wier. I'd like to make a comment on this point, because sometimes I think people ask about data quality, and what's really on their mind is relevance of the hazard.

I'd like to first state that the studies that are conducted preclinically are highly regulated. There are guidelines that very specifically indicate the number of animals, the type of endpoints. We have to vigorously justify the selection of the species. Why is that species relevant, why were those dose levels selected, demonstrate exposure in the animals and so forth.

I put it to you that rarely you will find a case for a current pharmaceutical agent where there's a question of data quality.

Now much more contentious is the issue of relevance of the hazard, because you could have a perfectly valid study that clearly indicates an adverse event in the animal, and that is what we call

a hazard.

Going back to Dr. Holmboe's presentation, he broke down risk into unwanted outcome and probability. Well, the toxicologists -- traditionally, we've talked about unwanted outcome as the hazard and risk as the probability that that hazard will occur under certain condition.

Now a key point in doing this is what we call hazard characterization. So the study gives us the hazard identification, but then, as David indicated in his presentation, sometimes additional effort is needed to understand the nature of that hazard and the conditions under which it actually could occur in the clinic.

Dr. Holmboe talked about hazard characterization in the context of permanence and time, but when we deal with developmental toxicity, there are many other aspects to hazard characterization that have to do with some of the characterization tool. For example, the pharmacodynamics -- A key question is: Is the developmental toxicity related to the intended

therapeutic target, because you know you're going to expose people to sufficient levels that are pharmacologically active.

There are a variety of other factors that have to do with interspecies differences. So as we go through this exercise, I think we should be clear that data quality generally isn't the problem here. Hazard characterization is the issue.

DR. JONES: Ken Jones, University of California, San Diego. You know, as a clinician I think, for better or for worse, one of the problems that we face or at least one of the major issues is that we tend -- and I'll cut straight to the chase -- We tend to discount animal data when counseling humans about teratogenicity.

I say for better or for worse, and it's probably for worse. I see you shaking your head, and I'm sure there's no question about that. However, one of the major focuses, it seems to me, of this working group is to come up with a way, and primarily for you folks to have them come up with a way to interpret your animal data in a way that is relevant for a

clinician or for a pregnant woman herself to be able to interpret that data.

To me, that really is the critical issue here. There's an incredible amount of animal data about the vast majority of drugs that are marketed, and for most pregnant women and for most clinicians today that animal data is totally discounted. I'll just tell you that straight out. It's discounted, because, in fact, we don't know how to interpret it.

In fact, if you look at the principles of teratology, it says that susceptibility for teratogenesis is based on the genetic background of the individual, and surely a rat or a monkey or a guinea pig or any other species that you folks have tested this drug in has a different genetic background than us humans.

So I think that this is a -- It's a critical issue that -- and you know, I look at your pregnancy integrated working group, and I would ask are there clinicians on that pregnancy integrated working group, people who know how to translate this information into a way that's useful clinically? To

me, that is really one of the major issues that we need to face here.

CHAIRMAN GREENE: That is a fitting comment, I think, to end the morning, unless Dr. Morse would like to respond.

I'd like to thank all of our speakers -- Oh, yes, please.

DR. HAMMOND: Mary Hammond, Raleigh, North Carolina. I had a question for Dr. Kweder, and it has to do with infertility treatment. That's what my area is.

We do so much where we give medications in the first trimester to our patients, and we use a lot of drugs that have almost become orphans, like progesterone and estradiol. I wondered who would go back and review that data for a new insert, since there isn't a company in particular.

DR. KWEDER: Well, that's a very good question, and that will be for us one of the challenges of implementing a new system with products that have already been out there for sometime.

We not only have the problem of many of

these products having categories that are maybe outdated or there may be additional information about. We have drugs for which there are no categories. A great example is amoxycillin. If a drug was approved before 1979, it doesn't have a category.

So a lot of generic products have no category at all or sometimes we find that -- and we're not sure how it happens -- different generic companies give them different categories, and we don't know how that happened.

So this is -- From our standpoint, it's very complex, but we do acknowledge that that's important, particularly because we know from studies that we have done that the most common -- and most clinicians know this as well -- that probably the most commonly prescribed products for pregnant women are those that have been on the market the longest. People have a sense of confidence in them, because they've been out there for a while, and their own personal experience has -- whatever that may be or however relevant it may or may not be, personal experience tells them that this will be okay.

So we -- I acknowledge that challenge. I don't have a firm answer for you how it will be done, but we recognize it needs to be.

CHAIRMAN GREENE: I'd like to thank all of the morning speakers, not only for a very clear and lucid discussion, and the panel members as well, but also for making my job easy and keeping our program approximately on time.

I'd like to break now, please.

(Whereupon, the foregoing matter went off the record at 10:20 a.m. and went back on the record at 10:43 a.m.)

CHAIRMAN GREENE: I'd like to call the committee back to order, please.

The next speaker will be Dr. Rachel Behrman, who will present the concept paper on labeling from the FDA, please.

DR. BEHRMAN: Good morning. As was just mentioned, my task today is to walk you through the proposal that we've developed, which as described would ultimately become a proposed rule for comment and rulemaking.

Before I do that, I'd like to try and give you some context and help you get some understanding of how we developed this. Why we're here today is clear to everyone. It's been discussed. We're here because no one is particularly happy with the current category system.

It's felt to be overly simplistic. It's felt to categorize drugs with dissimilar risks together. It's felt to give false impression of gradation of risk. It's felt to encourage, if you will, sort of not really sloppy thinking about these drugs, but boxy thinking.

Perhaps, most importantly, it doesn't encourage people who write labels to strive to ensure that people who read the labels know as much as we know. It almost encourages a kind of cursory approach.

The one encouraging thing that's come out of all of this is that people, in fact, are turning to labels to get this information, which means we have a great opportunity, actually, to reach these people and to provide them with this information and to do it as

well as we possibly can.

Before we talk about the pregnancy label proposal itself, first we have to think a little bit about labeling, because labeling is a very unusual endeavor, as those who have done it know.

The scope is enormous. It takes years to develop a drug, highly technical information. It takes companies months to put it into a new drug application for us. It takes us months to review it, and then we summarize it in several very, very thick volumes, and then we expect to be able to put this into a small package insert which we fold up and put into a drug box.

We do this with certainly underlying principles, that it be maximally informative but not necessarily comprehensive. It can't be. We don't have the space, and our audience doesn't necessarily have the expertise.

One thing that we typically do in the other sections of labeling is avoid speculation in the absence of information. So if we don't know, we say we don't know. If we don't know how it behaves with

renal impairment, we say that.

The pregnancy subsection is different, and it's different for a couple of basic reasons. The first is that generally, as has been mentioned, there's a lack of data. Typically, for a new drug on the market there's no human data.

That leads to an increased reliance on preclinical data, and there was just some very pertinent discussion about what those preclinical data mean and how much we know from them and how well we communicate what we know.

Then finally, unlike the other sections of the label, except for the information for patient section, we're typically writing for the health care provider. In this section we know that's not true. We're writing for the health care provider and for the woman, the pregnant woman or the potentially pregnant woman.

So that changes the rules a little bit, particularly this rule about not speculating. One recurring theme that we're going to ask you to think about is how much guidance can we give, and how

specific can that guidance be, when we really don't know very much?

These you have in your background package, and you've heard about. We were given some pretty specific suggestions or instructions. Replace the categories. That's pretty straightforward, as well as the last one, merge fertility, pregnancy and lactation into one section. That's pretty straightforward.

The others are much less straightforward: To provide more specific clinically relevant advice, again typically in the absence of information; to provide a concise summary of risk -- It's pretty tough to do if we're not entirely sure what those risks are; and provide more discussion of the data, perhaps a slightly easier task.

So what did we do? Well, we formed a multi-disciplinary group, and that came up. There's sort of the Noah's ark style. We came two by two. We had two pharmacologists toxicologists, two clinicians, two lawyers, and then a project manager to sort of keep us in line.

One thing that was clear to us is we

needed to provide a structure, because structure helps people find the information, and it helps people organize the information.

The goal would be that a similar body of information given to different authors would end up being pretty close. That helps people go from label to label. It helps people be familiar with the information. So we wanted to provide structure and organization, but it has to remain flexible, because, obviously, the bodies of data will vary tremendously.

Our two basic principles, somewhat coming from what we understood and somewhat coming from the public hearing -- One was to distinguish clinical advice from risk information, because we see those as very different, and to provide different levels of information for different needs, again because we know we're writing for a diverse audience.

So in our minds, the first cut we made, if you will, was to think about our information in three separate sections. I'll discuss each section in a little bit of detail. The first would be the clinical management statement. The next would be the summary

risk assessment, and the third would be the discussion of data.

It's important to point out, when we first envisioned this, we thought, well, maybe not every section would be either useful or possible to write for each drug. The more we thought about it, the more we thought that maybe we'd try and preserve each section for each drug, and that's something we're going to ask you to think about.

So first trying to tackle the clinical management statement: Again, this is where we put our really bulleted, pithy clinical advice, and that's easy to do in probably very few cases. If we know the drug is safe, we can say that. If we know the drug is completely unacceptable unless it's life saving for the mother, well, we can say that.

It's the middle that's really hard, when we don't know too much and we don't know exactly how to describe it. One way we've thought about this a little bit is one can almost divide these situations into six categories, but I apologize for the word, but six situations.

You think about women either are not pregnant women taking the drug but may become pregnant or they are pregnant when they're exposed to the drug. So that's two separate situations. Then you think about the very easy cases where you understand that it's safe or the very easy case where you understand that it's not really an acceptable risk except if it's life saving, and then the middle.

You can see that there are probably six kinds of situations we're thinking of, and one thing for us to think about with your help is whether we need to somehow in our guidance, probably not in the regulation that we write but in the guidance when we talk about how to use the regulation, whether we try to incorporate some standard language or suggestions for language.

Now just to give you a feel for what we were thinking of with this clinical management statement, this is a fictitious drug, Roselens, and this is how it would look under the current system, pregnancy Category C, should be used in pregnancy only if the potential benefits justify the potential risk

to the fetus.

This is an attempt to author a clinical management statement: Use of Roselens should not affect the obstetric or psychiatric management of patients who are in early pregnancy or considering becoming pregnant; women in the latter months of pregnancy should be evaluated for the need to continue Roselens therapy and, if continued, monitored for appropriate fetal growth.

Now this is a good example, because it demonstrates well how we need to struggle with this question of how specific we can be. So our question to you is do you think this is better? Is this helping? Does it help people? Do we need to define early pregnancy? Do we define late pregnancy? Do we need to define what do we mean by evaluated? What is the need? Under what circumstances would you need to continue this drug, and what's being monitored for appropriate fetal growth?

How much guidance do we want to provide physicians and patients, or is some of this something that really needs to be left to the judgment of the

people who are managing that particular situation?

The summary risk assessment would be the next section, and that's a little easier than the clinical management; because this is intended to be a concise overview of the risk information, not in incredible detail and more, if you will, user friendly, so slightly less technical, bridging the discussion of the data which would be highly technical, and the clinical management which resulted from the data.

There are a couple of problems we're going to ask you to think about: How to provide needed context, for example background risk; if known, the extent and the applicability of the animal data, which is something you've already started to talk about; and we're going to ask you specifically to think about the advantages and disadvantages and how to go about doing it, quantifying versus quantitating risk.

Again, it brings up the question of how specific can we be in the absence of tremendous information. So this would be the example: Based on studies in animals and human data, there is no known

concern for malformations or abnormal neurobehavioral functions -- and now you know the class of drug -- in infants born to mothers treated with Roselens. There is some concern based on animal studies for an increased risk of impaired fetal growth and late fetal and neonatal mortality when Roselens is administered during the third trimester of pregnancy.

One other thing for you to think about, because we will be asking you to comment on the overall format: Does it make sense to you to separate the clinical management from the summary of risk or are there cases where you would want to see that integrated?

Finally, a discussion of data which, in a sense, is the simplest, because we intend it to be a comprehensive presentation of -- It will be primarily animal data, but we stuck in human data at the last minute, because maybe sometimes there will be some human data, description of the sources.

Again, we have a question of how comprehensive we should be, because if there is too much detail, it won't be accessible. In that case,

where do we make the cut? Do we make the cut in terms of presenting all studies and simply limiting the amount of information or do we make the cut at presenting only some of the studies?

So this is our proposal to you for your consideration, and this is truly a work in progress. We're here for advice, for information, so that we can refine this.

There would be three subsections of a single labeling section. Three subsections would be fertility, pregnancy and lactation, and they would apply the same internal format to each subsection.

So the first would be clinical management. The second would be summary of risk, and the third would be the discussion of data. Obviously, we would need to provide careful guidance about how not to make this terribly redundant. If there is overlapping information, it should be in one place, and then cross-referenced to the other.

So in summary, our goals here are very clear. We want to write a label that's accessible, that's useful, that's informative, that tells the

reader what we know, no less than we know.

We want it to be relatively reproducible, so that we don't have highly varying types of labels for different drugs, simply because they came from different manufacturers or different review divisions within the agency. And we want some structure. We don't want it completely free form, but it has to be sufficiently flexible.

We're here to ask you how best to implement that, to comment on what we've proposed and whether or not it can be refined, and then it's important to point out, however, that whatever we do develop will need to be piloted, will need to be refined and improved, because this is something we really have to do right. Thank you.

Do you have any questions?

DR. BRIGGS: I am Gerald Briggs from Long Beach, California. That's a very interesting approach and a very innovative approach to -- or recommended approach to doing something different.

I have some questions, but I sort of get information from three different sources. I write a

book. So I'm always struggling to develop some method to present the data or the literature that it can be understandable.

Second, I get questions from physicians and other clinicians who read the books and ask me questions about it, and third, I get questions from patients, and I'm talking to pregnant patients, the patients who are actually planning pregnancy.

If you have -- and in each of these cases, I think, I hear a need for some human numbers rather than a lot of specific and detailed comprehensive animal data, but also some human data, and actually put the human data in there.

It's fine to have a summary. I think that's a great idea. I do that in my book. I put a summary at the end of most of the monographs, but I think you have to have the human data and specific numbers like this has been in ten pregnancies or this has been in 10,000 pregnancies or there have been epidemiologic studies or there have been none, or just case reports. I think you need that data.

DR. BEHRMAN: Yes. I think we -- There's

no question, we agree with that. We would expect in the discussion of the data to present any available human data.

What gets tough is then how do you put that human data in context. If it's been seen in ten pregnancies, whatever "it" is, should there be some discussion of what the background risk should be? There will be some interpretation given to the meaning of those ten human cases, because taken alone it really does not provide an accurate picture of what might be going on.

That's one of the things we really do want some feedback on, because that's a tough problem.

DR. DATTEL: Bonnie Dattel, Eastern Virginia Medical School. I have some comment about making specific clinical recommendations under the clinical management section.

There is really very little that is completely accepted as standard of care clinical management for a lot of what we are going to be addressing, such as surveillance for fetal growth, antenatal testing, an there are regional differences,

and there is changing information in terms of fetal monitoring, for example.

So I think that we have to err on the side of caution of not really providing a lot of clinical guidance in terms of pregnancy management and follow-up, because there is going to be such individuation throughout the country, depending on the pregnancy, other circumstances and, I'm sure, your lawyers probably.

DR. BEHRMAN: Exactly, and the companies' lawyers. Right. Exactly.

DR. DATTEL: So I think, you know, in the example that you use -- I mean, that, I think, would be problematic to provide that type of information.

DR. BEHRMAN: That's exactly the kind of feedback we need, but we need to even take you one step further and then say, well, do we include a clinical management statement when we have nothing to say essentially, and we don't know? What do we say?

DR. DATTEL: I think my issue would be the only clinical management statement that I would think is appropriate in drug labeling would be about the

drug specifically rather than follow-up of the pregnancy in the presence of the drug, because that -- There are so many variables for that, and it changes so rapidly that it would outdated very quickly.

DR. BEHRMAN: So in that example, you would then advocate saying something to the effect of describing what's -- that it may not present a problem, for example, in early pregnancy, and then what would you want to see said about later pregnancy?

DR. DATTEL: Well, provide the information. For example, it may be problematic in the third trimester or late trimesters of fetal growth, impairment, blah, blah, blah. Let the clinician make the determination about how that would be followed, because one person might say you need an ultrasound every two weeks. Somebody else says every month is fine, and then the person who has a problem because they didn't get one every two weeks, and there's nothing wrong with doing it every four weeks. I mean, everybody -- You know, it probably doesn't make that much of a difference.

I think, rather than being very directive,

I would just provide the information and then let the management scheme be developed individually. Because of a different medical problem, a different scheme would be developed, totally unrelated to the drug.

CHAIRMAN GREENE: This is Mike Greene. With respect to the process, who do you envision composing each of these summaries?

DR. BEHRMAN: WE joked that it would be nice to have one person sitting somewhere doing all of them. No, in fact, the process is -- The process in labeling is that companies will submit a proposed package insert with their new drug application and, depending on the quality of that, etcetera, it's heavily edited or not heavily edited.

In this section we would anticipate that there would be intense collaboration between the clinician, the pharmacologist toxicologist and the review division and the company. So for each drug it's going to be a different group of people.

DR. TAYLOR: Alan Taylor from Gilead Sciences. We've heard earlier this morning that framing the risk and the presentation of the risk

information is going to really impact on how that is viewed by physicians and patients.

I'm hoping that we're going to be moving toward some sort of standardization of the language to present this information. Otherwise, there will be huge problems in terms of cross-checking the information from one product to another.

DR. BEHRMAN: Again, that's very helpful, because that's something we've been kicking around, and we do need feedback on, because that is an option, a difficult one, however.

DR. ROSENE-MONTELLA: Karen Rosene-Montella from Brown. I have to disagree somewhat with another clinical perspective that was just presented, because sometimes just because there's regional differences or individual differences in how something is monitored or how something is cared for may not mean that that's okay or that that is the standard.

It may just mean that there are regional differences in approach or individual differences in approach. In a general way, to say something like monitor fetal growth, but not be so specific as to say

precisely how, actually gives the clinicians what they need to know, which is that you've got to monitor fetal growth.

I don't think there's anything wrong with that. I actually think it would be quite helpful and would bring up a standard of care, not bring down a standard of care.

CHAIRMAN GREENE: It doesn't seem to me that you disagree. I think that's what Dr. Dattel was saying, that specifying, for example, monitoring fetal growth without specifying exactly how you do it in precise detail is appropriate.

DR. BEHRMAN: Although one thing we struggled with -- and this is not just monitoring fetal growth -- for example, monitoring liver enzymes when we have a hepatotoxic drug, which is something we seem to have a lot of.

Using that example, we don't know that monitoring liver enzymes makes a difference. Yet we recommend it. What do we do if we don't know monitoring fetal growth makes a difference? Do we continue to recommend it? That has impact on the

economics, if nothing else.

DR. DATTEL: That is actually the other point I was trying to get at, not just the regional differences as a standard of care but the efficacy of a lot of these technologies are not proven. So I think we have to be just very careful in how we word it. Just provide exactly what information we want to provide without necessarily directly what the clinician is supposed to do.

You know, regional differences was just one example, but the technology issue was the other one that I used, because it changes so fast, and what we do may not actually cause a difference. This monitoring may not make a difference in outcome, as we're showing AFIs and all these other things. It probably won't make that much of a difference in long term outcome, but yet everybody spends a lot of money doing them.

So I just feel that we have to be -- As somebody who does it every day, I think we have to be very careful in how we word it. That's all.

DR. BEHRMAN: Right. Somehow targeting

that this is a pregnancy that needs to be watched without boxing people in.

DR. DATTEL: Exactly. You know, people who are exposed to different medications usually have some other issue going on anyway. You're taking antiretrovirals because you have a high risk pregnancy because of HIV, because you're already in a certain situation that's not referable to the general population.

DR. WIER: Patrick Wier. I want to make a comment and question about the summary risk assessment. I mean, in principle I think this is great. We have to be able to make conclusions in understandable terms from this myriad of data that we deal with regularly.

In the examples that were given in your presentation and in the booklet ahead of time, really, the bottom line of your summary risk assessment is either there is no concern or there is some concern.

DR. BEHRMAN: Or tremendous concern, I guess,would be another.

DR. WIER: That's my point, is at the word

concern. If you mean risk, don't use the word concern, because concern has the connotation of sensitivity to the issue. We're concerned about all these issues. We always are. There's always concern.

DR. BEHRMAN: You're right.

DR. WIER: What we need to work on is the type of narrative that can be used in these conclusive statements, and I'm also an advocate -- The comment was made previously that we need some standardization.

There can be some core statements that are used consistently. It's not that the labels are all going to be the same. It's not that we're reverting back to categories, but there needs to be a consistency of language.

If what we mean is that there is no expected hazard based on the preclinical studies, then that's what we need to say. We don't need to say there is no concern, because I'm concerned even in that case, because I've got a zero numerator.

DR. BEHRMAN: Right. No, that's a good point.

DR. MITCHELL: This is Allen Mitchell.

Can I interject a question?

CHAIRMAN GREENE: Sure, Allen. go ahead.

DR. MITCHELL: Actually, a comment. I'm not sure if it was resolved by body language that I missed, but when the question came up about whether it's appropriate to advocate monitoring procedures like LFTs or ultrasound for which efficacy hasn't been shown, to me, that's an easy one.

It would seem to me to defy logic to make that recommendation, that if an outcome or if an effect is going to be identified by some kind of monitoring procedure, there ought to be some evidence that that monitoring works. Otherwise, it's deceptive and cost ineffective and everything else that would be negative.

DR. BEHRMAN: The point is well taken. Thank you.

CHAIRMAN GREENE: Yes, please ?

DR. O'LOUGHLIN: Victoria O'Loughlin. I have two comments that deal with two separate sections from the green book that I read, the first being on the clinical management.

One of the things that I think concerns at least myself as a pregnant person that had a very bad pregnancy was early on detection -- you know, like you were saying, inadvertent pregnancy. If you're already on a drug and then you find out you're pregnant, one of the things that women hear a lot about today are things that are helpful prior to getting pregnant like folic acids and proteins that you're taking.

Maybe something that states the effect of this drug on those types of things that women have heard about, because I know there would be a concern, you know. Well, gee, if it ate all my folic acid, you know, does that mean I'm going to have a malformed baby, you know. Similar things like that might be very helpful in that section.

The second comment I had was in the data. One of the things that I think women are concerned about is a long term effect also on the growth of the child, not necessarily just the fetus but afterwards.

I was on a semi-experimental drug with one of my children, and she's four years old now, but my concern still is for her developmental growth and her

physical growth, both intelligently and physically; and I don't seem to see a lot of data that comes in after the fact on what's happening to those children after they've been exposed during pregnancy for some of those drugs.

The next comment I had was in terms of what other reactions, factors -- You had a list of factors, dosing, stuff like that. What other factors might be of concern if you're going to give a comprehensive report such as genetics or the interaction with other drugs that the person may have been exposed to at the same time might be helpful in a comprehensive report there. Thank you.

DR. BEHRMAN: Thank you.

DR. LEMONS: Jim Lemons, Indiana. That was a nice summary, too, of the proposal. This one on Roselens -- I had a lot of difficulty, actually. I kept looking at the proposal and hearing the discussion and the comments.

The questions are very important and intriguing, but so much depends on other information, I guess, that wasn't presented and gets back to the

quality of the evidence and the relevance of the evidence, as Patrick had said.

For example, the conclusion here was that fetal growth retardation may be a significant side effect, risk, in third trimester, but it was only based upon animal data. Dr. Jones said very effectively articulated the concerns about that.

That could cost a tremendous amount of money, because a rat or a mouse demonstrated growth retardation in late gestation. I guess one would ask what's the biologic possibility of that? What is the quality and the relevance of all the evidence in the animal model, and should that be considered in proposing something that may or may not be relevant to the human?

If this drug is, for example, used to treat hypertension, hypertension itself, we know, is associated with fetal growth retardation. So has that been established that, in fact, it's an increased risk in relevance in the human pregnancy?

Are you, as you have mentioned, good alternative therapies? And these change with time.

It points out the difficulty, I guess, of keeping these updated and current, because now, of course, there's a lot of interest and initiative and incentive for pharmaceutical companies to provide data both in children and in pregnancy which will make this an ongoing process.

I think there will need to be some obligatory, regular review of current literature, and I think it should be incumbent upon pharmaceutical industries to monitor and report and modify, I would think, as new evidence becomes available; because the human data, as Dr. Briggs said, is what's important insofar as we can tell now.

DR. BEHRMAN: Those are a couple of very important points. I think it's worth noting, one, that the problem in terms of keeping labels current is not restricted to the pregnancy section. It's something we're keenly aware of and working on.

In terms of the perspective on the animal data, I think we're going to asking a specific question about what to do with all the animal data and whether you as a committee advocate sometimes making

a cut and saying, well, we -- we, now the reviewers and the company together -- don't make much of this; we're just not going to put it in there, because we think it's just going to mislead people, for example. That's something to consider.

CHAIRMAN GREENE: Dr. Cragen, you had a question?

DR. CRAGEN: Just a fairly simple comment, sort of related to Victoria's here. When I was reading through the examples in the green book, I know we're focusing on pregnancy here, but fertility, pregnancy, lactation are sort of a continuum in thinking about an inadvertently exposed pregnancy.

I found it a little bit awkward to go to each section to get a risk assessment, and I wondered about just organizationally putting the summary for -- you know, with those three headings underneath each, so you had a risk assessment or a data summary, whatever, for all of --

DR. BEHRMAN: Altogether?

DR. CRAGEN: -- parts of pregnancy together.

DR. BEHRMAN: That's another approach, and we're certainly open to that. I think we feel that there are really benefits or risks, if you will, to both approaches.

CHAIRMAN GREENE: Yes, please?

DR. WISNER: I'd like to return to this animal data issue. As a clinician, I generally allow the discussion with the patients to focus on human data, because I think that the human data, as was discussed earlier, has to trump animal data.

As also has been discussed, there are a number of kinds of outcomes for which no human data exists, and I think in that case, presenting some animal data for those categories is important.

So I think it may -- What we might want to do depends more upon what we have in the quality of the data rather than making a blanket statement that we don't want to deal with animal data.

CHAIRMAN GREENE: One last comment, and then I think we'll move on to the next speaker. Please?

DR. DeGEORGE: I would be very interested

in actually hearing something from the committee's perspective on the notion that most of the time when the product was first approved, we have very little, if any, human data. That's when the label is at least first written.

We can go back, and we can update it with the human data, but in the absence of human data, which is what we're usually dealing with when the product is first approved, what should be in that first label?

DR. BEHRMAN: Joe is definitely not asking me.

CHAIRMAN GREENE: I'll reply to that from my perspective, and I think the only thing that can be said is that there is no data. I don't think that you can go beyond the data, if you don't have it.

If there is animal data which seems credible, which has biologic plausibility, which at a reasonable dose ratio shows significant concern or risk, as Pat would say, that would have to be presented as well. But the fact that there is no human data per se must be specified.

One last comment. Then we'll go on.

MS. CONOVER: Beth Conover. I actually -- to stir things up, at the Teratogen Project we use one more piece of data besides human and animal reproductive data, which is kind of a hypothetical which might be the impact of this agent on an adult.

So is it a vasoconstrictor? Does it cause bilirubin problems? Does it -- So that we're kind of extrapolating. You wouldn't do that when you had good data on human experience during pregnancy, but when you don't, then you start to look at some other factors. This is a carcinogen. I mean, you start to put other things in, like mechanism of action or adverse impact on an adult.

I know this actually came up in the hearings that occurred before, that someone suggested that data might be included as well.

CHAIRMAN GREENE: Okay. Thank you very much. I'd like to move on now to Dr. Aikin's presentation, please.

DR. AIKIN: Good morning. My name is Kathryn Aikin. I'm a social science analyst in the

Division of Drug Marketing, Advertising and Communications in FDA's Center for Drug Evaluation.

I will be presenting the results of two physician focus groups that were conducted in February of this year.

Focus groups are a qualitative research tool, and they are useful for identifying issues of concern to relevant populations. Focus groups can also be used to formulate questions that can then be answered by using more quantitative means.

It is important to note that qualitative research of this kind is not generalizable to the population at large. However, it is very valuable for narrowing broad topics which can then be examined in a quantitative manner.

The purpose of the two focus groups conducted in February was to provide feedback on the proposed changes to the pregnancy section of drug labeling, and we just used drugs.

Next slide. Fifteen MD's were recruited from the 15th Annual Clinical Update in Obstetrics and Gynecology Conference, February 9-12, 1999. The

majority of participants at this conference practice in the northeast.

Eleven OB-GYNs, three family practitioners, and one reproductive endocrinologist were recruited in advance, and each focus group lasted about one hour.

Participants were provided with the pregnancy section from three fictitious prescription drugs. Each label was presented one at a time. The first label was designed using the current format, which you can see on the lefthand side of this slide, and the other two were designed using the variations on the proposed format, which you can see on the righthand side.

The discussion of the label centered around four areas -- next slide, please: The current thinking -- what factors do they take into account when prescribing during pregnancy, and what information do they currently rely on; the availability of information -- the presence, absence and/or quality of animal and human data; an evaluation of the sample labeling -- their overall impressions,

opinions about the format, and the clinical management section, in particular; and finally a wish list -- what sort of information would they like to see in this section, and any other suggestion they may have had.

Next slide. To begin with, current thinking: The groups indicated that they rely on the pregnancy category as a guide for prescribing and, as one participant said, it's an easy reference. But they also tend to rely on colleagues for advice.

This was particularly true of the family practitioners and, as one participant said, the tendency is to use things that have been around. Nobody wants to be out there on the forefront finding 15 years later they made a mistake.

Next slide. Regarding the availability of information, the participants strongly indicated the need for human data, and I think we've heard that a lot this morning. They were willing to accept animal data in the absence of human data, provided it was presented in terms of human dosage.

"They just tell you they gave X amount,

and you have to go back a couple of pages, look at the regular dose we give our pregnant patients, and what does that mean in a rat compared to humans?"

Next slide. In terms of format, the participants preferred the format of the proposed labels over that of the current one, saying they would like the recommendations up front, followed by the details.

"I'd like to see someone make the summary statements that are in this for quick reference, right at the top. I hate to read in a couple of pages if I don't have to."

"It gives you the reference if you want to look up the study and make your own conclusion."

Next page. Second, they espouse a desire for uniform labeling format across drugs. There is a lot of inconsistency from drug to drug. Sometimes you don't find what you're looking for. A more standardized format would be very useful.

The clinical management section: Much of the discussion was focused on this clinical management section. participants were generally favorable toward

t he clinical management section. "The first paragraph tells you how to manage. You don't have to read past the clinical management if you don't want to."

"It's like a newspaper article. The important information is up front."

Next one. The two sample labels in the proposed format varied in their directiveness for clinical management with one being much more directed than the other. Example 1 reads: "The clinical management of patients who are in early pregnancy and taking or considering taking Roselens should not be affected. women in the third trimester should be evaluated for the need for continued therapy and monitored for appropriate fetal growth>"

Example 2, which is slightly more directed reads: "Women who are taking Leural and become pregnant should be advised to consider discontinuing the drug and may warrant evaluation for fetal effects by sonography. Women who are considering pregnancy should be advised to consider alternative treatments for asthma maintenance."

Next slide. Now, interestingly, OB-GYNs and family practitioners came out on opposite sides in terms of preference for these two. OB-GYNs really disliked the directive language. "The statement evaluation for fetal effects by sonography is saying they should all get ultrasounds. Think of the lawsuits."

Fear of law suits was a topic that we heard a lot from the OB-GYNs, and they -- I don't have it on this slide, but they made the point that not only are they reading the labels, the patients are reading the labels, and their lawyers are reading the labels. But family practitioners wanted to be told what to do. They liked the directive language.

"What is the bottom line? Is it red light, is it green light, is it yellow light?" In fact, we had a lot of discussions with family practitioners and the OB-GYNs in the focus groups. They were asking the OB-GYNs, okay, if it's this, what do we do? Next slide.

Finally, we wrapped up the discussion by asking participants if there were things they would

like to see in labeling or things they would change about the current labeling.

The participants reiterated the desire for a uniform format across drugs. They would like to see human data where it exists, but they did say it was okay to say there wasn't any, if there were none.

They would prefer to see animal data arranged by species with human at the top. They suggested dividing information by trimester. They expressed that more information is better, and finally, they stressed the need for a bottom line, placing the most important information up front, and preferably under clinical management.

Thanks. Are there any questions?

DR. JONES: Ken Jones. I'd like -- I think, obviously, your two talks, the last two talks are very much -- Yes, obviously, these last two talks are somewhat similar in terms of what they're getting at. But I would like to sort of be a devil's advocate for a minute and ask whether there really is a reason for this clinical management section, that maybe that could be left out, despite the fact that everybody

liked it.

I wonder -- It almost sounds to me as though their clinical management is for obstetricians, and the risk assessment is for the person who is going to be evaluating the baby, and they basically are the same thing, and I wonder why we need the two sections.

So if you could articulate that, or the last speaker, maybe that would help me. Aren't they both speaking to the same issue, really?

DR. AIKIN: Rachel, do you want to address this?

DR. BEHRMAN: That's one question. Actually, it's an open question. You can tell us you think they should be merged into one. That's a reasonable point. What we were thinking was a quick, pithy, never use this unless it's going to save your life, use it without any concern of risk, or whatever would be appropriate.

Also, technically, for us that would help us, because then if we wanted to move it and repeat it higher up in the label to give it increased prominence, we would know exactly what to extract.

That would make it very simple, and that probably influenced our thinking as well.

For example, let's say this was a drug that actually should not be used in pregnancy. One could think of, for example, thalidomide. We could just extract that sentence, put it up front very prominent in a box or whatever else you wanted to do.

So that was part of our thinking. The other -- And then we were also trying to respond to the recommendation that we had different levels of information. So this was a very simple, very short, digested recommendation, followed by a somewhat more involved discussion of risk.

As I mentioned, when we originally thought of this, we thought that a clinical management statement would not always be possible. There will be times it simply could not be authored, and then it would be omitted, and that's also a proposal that you could think about, whether there are times when such a short little synopsis is useful and there are times when it's not, in which case we could try and think about how to incorporate that into the proposal and

into guidance. But that was our thinking, and it may be that the opinion of the committee is that that was not such good thinking, and that we should, in fact, combine them.

Does that help?

DR. WISNER: I think this issue of clinical management is an interesting --

CHAIRMAN GREENE: Please identify yourself.

DR. WISNER: Oh, I'm sorry. Kathy Wisner.

I think the issue of clinical management is an interesting one, and I think to some extent it depends upon the issue, and they may be broad.

For example, there are certain medications that could be given to pregnant women that interact with the particular physiology of pregnancy. An example is tricyclic antidepressants where we showed that the metabolism changes across pregnancy.

So one could envision putting that in as a way in which the drug interacts with the pregnant state as just a statement, and allowing the treating physician to make what use of that they can.

To me, that seems somewhat remiss. Suggesting a clinical management plan for that situation with serum levels seems to be appropriate, because if those serum levels are not sustained, then the response is lost.

So I think it may depend upon the specific situation.

DR. KWEDER: I want clarification on that, Dr. Wisner. Can I ask you -- I just want a clarification on that.

Are you saying that, for instance, in a clinical management statement that you would find it helpful -- There is a separate section of most labels that deals with pharmacokinetics and dosing, but are you saying that it would be helpful to make some comment in the clinical management statement to alert the clinician this is something that they may have to be concerned about, even if detailed information is in another section?

DR. WISNER: I actually haven't seen pharmacokinetics or pharmacodynamics related to pregnancy in that other section, and I guess what

would be helpful is taking that data that's related to pregnancy that interacts with the pregnant state relative to that particular drug.

Again the two possibilities are making the statement about the data and leaving the management to the obstetrician, but for many drugs that leaves the obstetrician with, well, that same question, what is the appropriate management, what am I supposed to do?

So I think putting a directive in about obtaining serum levels and managing serum levels, which is a clinical management strategy, seems to me very appropriate.

DR. DeGEORGE: Joseph DeGeorge. I just wanted to make another point about one of the rationales for at least our attempt to separate the summary risk section from the management section.

Part of that was the comment that -- and the criticism of the categories which lumps together risk/benefit and sort of rolls them all up into one, an A, a B, a C, an X. This was the case of trying to say what is the risk separately, and acknowledge that the risk -- the management of the patient may differ

very greatly even given a specific risk, because of the indication, other factors.

Sometimes there are multiple indications for products, and you wouldn't want to give a general risk/benefit statement that tried to wrap them all into one.

DR. BRIGGS: I am Gerald Briggs, Long Beach, California.

Relating to the question on pharmacokinetics, I think it's pretty true that pregnancy affects the pharmacokinetics of every drug in one way or another. In most cases the drug is excreted a lot faster or is spread out in the huge volume of distribution that occurs in pregnant women.

Again going back to what probably is a rule of thumb again, if you have to do drug levels in a non-pregnant patient, like dilantin or any of the immunoglycosides or any of those agents, you certainly would do them in a pregnant patient.

DR. DATTEL: I just want to respond to --

CHAIRMAN GREENE: Identify yourself, please.

DR. DATTEL: Bonnie Dattel, Eastern Virginia Medical School.

The issue -- Clearly, the statements about pharmacokinetics and pregnancy are true, but there's really not very much data. For example, anti-seizure medications -- whether or not the efficacy is altered or whether or not you should actually alter your drug dosage regimen in a patient who clinically is not having seizures.

There is some debate at least within the perinatal community about, just because your blood level is low and you haven't had a seizure in nine months, and you're pregnant, should you actually up the dosage of a drug that may actually have a problem.

So I think there are some issues about, because there isn't data available readily about not just all the pharmacokinetics of these drugs but also about what the clinical outcomes are in pregnancy. I guess I'm going to probably beat the same drum.

I have a real problem with us taking on a role of -- in drug labels, writing a textbook about clinical management on patients. I think the role is

to provide the information but not outline for everybody how they're supposed to manage every pregnant patient on a certain drug.

I think that's not, to me, what the role of a label is.

CHAIRMAN GREENE: Dr. Chong, I think you had a question.

DR. CHONG: Dr. Chong, Albert Einstein, New York.

I'm going to put on one of my other hats for discussion. One of the things that we are very aware of, are there risk management issues in utilization review, and there are lots of third parties and other very interested people in looking at how we practice.

So one of the things I also do is I defend the hospital in risk management cases. So one of the very poignant things that came out in the last two discussions is the use of labeling and the use of labeling in terms of prescribing practice.

That's why I was particularly interested in the clinical practice section, if it outlines a

standard of care versus reflects a standard of care or if it is not a standard of care, impacts very heavily on the cost of practice of medicine and the regulation of medicine, especially through peer review types of situations.

DR. BEHRMAN: Could I comment? We're very conscious of that. We're very conscious of the impact that drug labels have in terms of reimbursement, in terms of -- and we try very hard to stay away from specific and specifically unsupported recommendations. That's a problem not just for the pregnancy section but all sections.

If I could just ask one question of the committee along this vein. When we discussed this proposal before the reviewing division directors, there was some enthusiasm for a statement such as "seek the advice of an expert."

Does the committee find that approach -- You all laugh. Okay. But remembering that these were not exerts on pregnancy saying this, is that something that -- In other words, there is some concern that for a pregnancy that's going to be very complicated or

using a very complicated therapy, potentially dangerous or risky, should we, the FDA, be providing that kind of advice, that maybe average care, standard care is not quite enough here, or is that again not territory you would want to see a label getting into?

CHAIRMAN GREENE: Dr. Briggs, did you have a comment? You want everybody to call you?

DR. BEHRMAN: We'll take your number and just stick it in.

DR. BRIGGS: On perinatal pharmacology, which I teach at times to medical students at University of California, it is a very complex subject. But I don't know if this vehicle, pregnancy labeling, is the place to put that subject.

I think in the ideal world, if someone were to prescribing a drug to a woman of childbearing age, that person -- or recommending a drug -- that person would definitely consult every information source they could find.

I don't think that happens, which is why we're sitting around this room today. But I don't think perinatal pharmacology is the place to put into

the pregnancy labeling. I don't think that's the section where it should go. It's a different issue.

DR. LEMONS: I would agree. The question -- Jim Lemons. The question of standard of care, obviously, comes up in all of these guidelines, and is it an optimal standard? Is it a minimalistic approach? Does it encompass 95 percent of what's considered reasonable practice?

It's very hard to articulate that in sufficient detail in a statement like this, and it does present problems in what the clinical management section -- how broad it should be and if it's a problem when there's renal disease, for example, how specific do you advise using this drug.

When there's renal disease, then you should do this, this and this, or using it when there is liver disease, there should be this, this or this. It's hard for me to grasp, I guess, the scope of what might need to be put in here. That might need to be defined better.

DR. MITCHELL: It's Allen Mitchell. Can I interject?

CHAIRMAN GREENE: Sure, go ahead, Allen.

DR. MITCHELL: To respond to the question -- I don't know if it was Dr. Aikin who asked about the recommendation to seek expert guidance.

I favor that strongly in situations where the data aren't clear-cut. I think what it does is serve as a reminder to the practitioner that, if he or she isn't really comfortable with their understanding of the issue, that they do have an obligation to get further information.

This isn't a simple issue, by any means. I don't think that would be necessary where either there's no information known about risk or, you know, the risk is so clear that you don't need to seek expert advice. But I think in selected instances which may be the majority where there are some suggestions of potential risk, whether it's animal data or incomplete human data, I think that would be very helpful.

CHAIRMAN GREENE: Dr. Wisner.

DR. WISNER: Thank you. I have two comments. One is I think what we may be struggling

with is what's really the core function for this classification scheme.

I mean, coming from a clinical bias, mine is that the function of this classification scheme ultimately is to improve the physician's ability to care for the pregnant patient and improve outcomes for those women.

So that leads me to make a strong recommendation against taking a blanket statement or a blanket position of we will, therefore, recommend no clinical management strategies at all. I think that, as was given example for seizure disorder, there may not be clear evidence that monitoring or changing dose creates any effect.

That certainly isn't true for the tricyclic data that I gave you where, in fact, we documented emerging clinical symptoms when the serum levels dropped.

So again, I think, if we're out to really improve clinical care for female patients, leaving that information out or saying, well, they'll consult a perinatal pharmacology book, particularly when we've

heard from the focus group that they want the information up front and that's it, they're going to just consult that information, again seems to me to be remiss.

DR. ROSENE-MONTELLA: Karen Rosene-Montella from Brown University.

You can tell we're falling out on the side of -- It appears to me that a clinical management section would be very helpful. When I think about that, I was thinking a couple of other things that that kind of section might address, might address some of what's going on here, which is that that section may not just be aimed at an obstetrician, that the obstetrician is not the only person that ends up having to make decisions about prescribing to a pregnant woman.

So there's all the other areas of specialties of medicine where that will need to be addressed. So it may not be somebody who is as familiar with fetal risk or how to monitor a fetus or something like that, but somebody who is very aware of a medical illness, for example.

So I think that there's an opportunity there to address that you have different provides reading that section.

Additionally, that may be a place to address what will happen if someone is not treated. I think, in the vein of Dr. Wisner, we're thinking of how can you go ahead and take care of people? How can this information be used to feel comfortable providing care that needs to be provided?

One of the ways to do that is to look at it as an opportunity to talk about what will happen if someone is not treated. A seizure disorder, uncontrolled seizures is an excellent example, because hypoxemia and acidosis for a fetus may be much worse than a drug exposure to that fetus.

There's series of medical illness for which that's true.

DR. BEHRMAN: Just as an aside, we actually envision the clinical management statement more for the -- well, not specifically for the obstetrician, but in fact -- So it's interesting the feedback that we're getting is that you thought we

intended it for the most sophisticated reader.

DR. DATTEL: I actually don't think we're disagreeing. I think more what we're disagreeing --

CHAIRMAN GREENE: Please identify yourself, Doctor.

DR. DATTEL: Bonnie Dattel, EVMS. I forget that.

I'm not disagreeing that there should be a clinical management section. It's more of the content of it and how directive it is. I think information is important, but directing that, you know, serum levels need to be followed every two weeks, blah, blah, blah, you know, leaves -- That may not be necessary. You know, there are other factors.

I think it's not so much that the information should be there as how the information is given and how directive it is and how specific it is, because if you are a family practitioner or a nurse practitioner or a dentist and you're prescribing -- you want to give tetracycline to somebody, for example, for dental surgery, and you see there are some issues, you should call somebody else. You

shouldn't be given Step 1 through 10 to do or follow this and that and the other thing.

So I think the directive part of it is more what I object to rather than the information. I think information is important, but how directive -- I don't think that's the role of the label, to be directive.

CHAIRMAN GREENE: Mike Greene. I have a question for our staff people from the FDA, which is: One of the problems and issues that's been raised repeatedly throughout the morning is the frequent lack of information with respect to human exposures at the time the drug is marketed.

My question is does the FDA have any thoughts or plans to encourage or require any kind of information, testing, studies in humans before a drug is marketed or the label is written?

DR. KWEDER: Well, Rachel is the Deputy Director for Office of Medical Policy.

DR. BEHRMAN: Thank you so much, Sandi.

We have certain -- As a regulatory agency, we have certain tools. There are certain things we

can and can't do. There aren't that many things we can actually force companies to do in studying pregnant women. This is probably not one of them.

We do -- I'm saying that somewhat facetiously. We see the critical need for more information, and we see other approaches, and we are trying, in fact, to encourage companies -- It's to everyone's benefit, to theirs, to the health of the public, etcetera.

So if your question is do we recognize the need, we certainly do. Are we making a concerted effort to, one, try and see that the data are developed and, once developed, see that they are incorporated in the label? The answer is yes.

The third question would be is it easy to accomplish, and the answer is no. Does that --

DR. KWEDER: I can add to that. The likelihood that there will be a directive requiring study in pregnant women is pretty slim. We would probably never -- It would just probably not happen.

We have had enough difficulty getting good or substantial inclusion of women in clinical trials

for most products in general, never mind pregnant women, and we have a system in place now that finally requires -- after many, many years, finally requires companies to address pediatric development at the time of an application for marketing is submitted.

I think the likelihood of that happening in the near future for pregnant women is slim. On the other hand, we do feel that this is important, and we have tried to address this in several ways.

One is through the suggestion of trying to select what products would be appropriate for observational studies post-marketing, pregnancy registries. They are not the answer to the big question, but in some cases they may provide some information. They're better than nothing, as far as we're -- in many cases, if they're conducted well.

That's why we've gone forward with a document on establishing pregnancy registries. We have also worked a little bit with one of our sister agencies, the NIH, to try and find ways through their clinical trial system to actually get products that we know are commonly used in pregnant women at least

studied in Phase I to look at the clinical pharmacology and the pharmacokinetics and dosing.

To date, none of those studies have -- I mean, we've been working on that for a while, and it's been extremely difficult trying to get any of those off the ground. To my knowledge, none have occurred yet, but those are the kinds of things that, if we saw a need, we are very happy to sort of wave the flag and try and get companies to do those sorts of things, particularly -- I mean, we can all think of products that are commonly used in pregnancy about which there's very little data.

DR. BEHRMAN: But one thing this is part of is to make sure that the labels we have actually reflect the information that's available, because currently that's not the situation, and that's certainly something we can fix.

DR. BRIGGS: There's an incredible organization here in North America. That organization is Teratology Information Services. Actually, there's two representatives here, Beth and Jim Jones down here. They are members of that. I am, too.

This is a group that goes across all of North America at various university hospitals and medical schools to answer questions from the public on drug questions or other exposures, chemical exposures or environmental exposures.

Since most of the exposures to new products are inadvertent or just started without knowing the patient is really pregnant, then these patients have questions. So this organization is really situated so well to bring up and pick up this information so quickly, much faster than, say, setting up a surveillance study by a drug company, that they just have the opportunity, if they are used properly, to gather that data and have it out in a year or two after a drug comes on the market.

DR. KWEDER: Thank you for that comment. We actually fully appreciate that, and we are also in the process of looking at ways to try and think more creatively about pregnancy registries in terms of, you know, thinking about the poor clinicians out there who have many pregnant women on many medical products. Just the logistics of trying to contact many companies

-- are there ways to make that easier through an organization like OTIS or something else where things could be more centralized? But that's in its infancy.

DR. HAMMOND: Mary Hammond. Are we taking full advantage of international data? I know that a lot of the drug studies for when they are released have to be done in the United States, but are we looking at international data for human pregnancy results?

DR. BEHRMAN: There is no requirement to study a drug in this country, and we look at all sources of information.

DR. DATTEL: I have a question. Bonnie Dattel, EVMS. I have a question.

Dr. Chong actually brought this up, and it's something I had written to myself on here in terms of logistics and what we recommend. We often will prescribe things based on data and information, but because of managed care and utilization reviews and everything, the drug is not available to the patient.

I think it might be helpful -- and

basically, you have to go outside -- the patient has to pay out of pocket and all those other kind of stuff, even though it's the best drug and the least risky drug in whatever information we have.

Are insurance companies or managed care organizations involved in any of these issues with you, and two, is there a way that, if this is the best alternative at present or if there are many other options that are equally as efficacious and safe, that we can include that somewhere on the label so that the justification for the patient in terms of utilization through HMOs and things is not necessary? The patient doesn't get stuck paying for the best drug or taking a riskier drug.

DR. BEHRMAN: One thing we're very careful to do is try not to make the label an obstacle to reimbursement, because that often can happen. One thing we're struggling with -- and I sort of alluded to it during my discussion -- was what to do about therapeutic alternatives.

It's very hard for us to say in a label try Drug Y, although we probably can you should think

about alternatives, and that's something we'd like to hear from you.

In terms of actual reimbursement, that's really not something we have any authority to become involved with.

MS. CONOVER: Actually, the issue of alternatives is really interesting, and it also deals with like, oh, let's say in an asthma drug, taking the drug Oreli versus inhaler, which is something you're thinking about for the woman herself and her side effects, but again a strategy we use all the time in terms of lowering the dose and sometimes the risk to the fetus.

CHAIRMAN GREENE: Mike Greene. I have a question which may be unfair, because the scope of the current project is daunting enough. But have you -- Has the FDA given thought to a formal process of review and revision, either periodic as a set of amount of time goes by or if sentinel or important information should become available in the interval?

DR. BEHRMAN: This is a global problem for all sections of labeling. Yes, we are thinking about

a variety of different ways to approach it to ensure that all sections remain accurate and up to date, and that outdated information is removed as well.

So, yes, it's part of the daunting project. As Sandi alluded to before, the implementation is, in and of itself, a nightmare, but we'll have to -- The plan for implementation will have to include a plan for updating.

DR. CHONG: Dr. Cong, Albert Einstein, New York. A totally unrelated issue.

In the role of labeling, we've looked at the issue of reproduction through its continuum. The other thing I was wondering if labeling could address was the continuum through the age of women.

Women who are early adolescents who are pregnant may have different needs than women who are in their thirties and forties, especially from the pharmacokinetics point of view or in growth and development, and whether or not labeling should address any of that.

DR. KWEDER: I am not sure. Can you be a little bit more specific about what you're getting

at?

DR. CHONG: Oh, in municipal populations where I work, there are a lot of women who are 14 or 15, and they are pregnant, and they are also, I think, developmentally perhaps not the same as a woman who is in their thirties or forties.

We have to pay a little bit more attention to the fact that they themselves are still growing in many ways, and that whether or not labeling will in specific cases, if it's specific to a particular -- relevant to a particular medication, address that.

DR. KWEDER: We do -- We will specifically address information that we have on -- I guess we're talking about the adolescent. The adolescent pregnant patient is a whole - is yet another cut on adolescents and pregnancy and where they overlap.

I think it's a good point. If we know, for instance, that adolescents metabolize a product differently than adults, pregnant or not pregnant, then we ought to be thinking about how that might affect the adolescent who is pregnant. You know, what other kinds of things do we need to consider?

A lot of this will come down to being applied or thought about, depending on the individual drug and what it were likely to be used for, in what patient population. So we do try to address some -- definitely are increasingly going to be addressing pediatric issues, but you raise another -- It's an item for us to think about in considering this pregnancy section of the label, because you're right.

The perimenopausal woman -- pre-menopausal woman who is pregnant is probably a lot different physiologically than the 15-year-old.

DR. ROSENE-MONTELLA: I'm just thinking that we're over and over again hearing how desperately we need more human data, human information, and again that often we won't have any when something is released.

Rather than just a simple registry, could we take advantage of this committee and collect -- Could the FDA do something to facilitate the collection of information of drug exposure to our pregnant patients? We've got huge populations of pregnant patients, just the resources here. We see

10,000 deliveries a year where I am.

I know that, if we ran around the table, you've got a lot of information on a lot of exposures here. Is there a way to use the resources of this committee in conjunction with you, with pharmaceutical companies, to establish that kind of registry like that's done formally?

DR. BEHRMAN: It's something we'd be happy to consider how it could be implemented. We could think about it. It's a novel idea. It's not typically -- It's not something we can do on our own. It's just -- We're not set up for that, but something, certainly, we would be interested in trying to participate in. I don't know if you have additional thoughts.

DR. O'LOUGHLIN: Victoria O'Loughlin. I just wanted to touch on something that -- I can't see your name, but at the end of the table there -- talked about as far as a drug that might not be available because of managed care or something like that.

In the clinical management section, could there be something like an Excel spreadsheet or a

reference guide of similar drugs that are associated with fixing whatever it is that you're trying to address at the time, such that maybe the clinician would have a choice?

DR. BEHRMAN: Right. There are a couple of obstacles to that. One is size of the label, and the other is we generally don't put things in labels unless they are supported by very specific data.

So, for example, if there were a comparative trial of this drug in pregnant women, we could put that in, but more than that, I think we probably would be limited to some discussion that the practitioner and patient should think about alternatives, without actually naming those alternatives.

DR. BRIGGS: It might just a good time -- Gerald Briggs, Long Beach. It might be a good time just to remind myself and others that this is a very complex subject. If you look at all birth defects, we still don't know what the majority of birth defects -- what causes them.

I mean, there's no known cause of those --

for the majority of birth defects. For example, we have a drug like hydrocortisone that's been around for 50 years, and we've known that it caused oral clefts in rodents for 50 years, and yet if you ask most clinicians nowadays if it causes oral clefts in humans, they would say no. But there's been two huge epidemiologic studies, one in Spain and one in Hungary that took in 3 million patients, and found a fairly high statistically significant increase in oral clefts in humans who were exposed to corticosteroids.

So the relationship looks like it's very positive, and although it's a very small risk, it's still a positive risk. But here's something that the data has been there for 50 years, and we're just now getting around to the point of saying, yes, there is this to this drug.

So we may be kidding ourselves if we say we can come up with an objective, straightforward answer to any drug, whether it causes birth defects or not.

DR. MITCHELL: This is Allen Mitchell, if I can interject.

CHAIRMAN GREENE: Yes, please, Allen. Go ahead.

DR. MITCHELL: I agree with what Dr. Briggs was saying. I'm not sure I agree with the interpretation of the studies, but that actually just reflects one of the continuing dilemmas, is how you resolve differences in interpretation of studies.

It seems that it's inevitable for ethical and other reasons that, when a new drug comes onto the market, there can't be any human data, other than serendipity, with regard to birth defects. It also seems that the primary function of the insert is to give as much information, but recognizing that full information probably will never be available.

Many of us would argue that it's not sufficient to look at a cohort of 100 exposed women, finding no increased risk of birth defects, and say the drug doesn't increase the risk of birth defects. It could well increase the risk of oral cleft substantially or any other specific defect, and it's unlikely that in any short or reasonable period of time we're going to have sufficient information on

large enough samples to rule out even reasonable increases in risk of specific defects.

I think one of the purposes of the label has to be to communicate that dilemma to not only the practitioner but the patient, and it's a real tough challenge.

DR. BEHRMAN: If I could add to that, because it was mentioned before and communicates some level of understanding of the uncertainty associated with that risk.

CHAIRMAN GREENE: I have a question, and that is: Many years ago when the FDA first started regulating drugs, it was sort of a daunting project to try to review everything, and there was a consensus on a group of compounds that were generally regarded as safe or GRAS substances.

Is there any thought in this project to grandfather or grandmother in any compounds or drugs or will everything be reviewed anew?

DR. BEHRMAN: It's a little different here, because we're not -- There's no regulation from which these drugs would be exempt. The question is do

we want every drug appropriately labeled, and the answer is yes.

Then the second question would be can we do them all at once, and the answer is no. We're going to have to prioritize them, and then we'll have to figure out quite how to do that.

CHAIRMAN GREENE: I had one other question. That is with respect to compounds that are not quite drugs but yet they are drugs. So, for example, alcohol used as the vehicle in a cough medication is not the medicine per se, but is an integral part of the preparation.

Is there a risk or a concern or a thought about worrying about those things?

DR. BEHRMAN: On over-the-counter or prescription drugs?

CHAIRMAN GREENE: Either one. I mean, alcohol would be used as a vehicle, and there are other compounds that are used in vehicles.

DR. DeGEORGE: Well, that's part of the -- Joseph DeGeorge, FDA. As part of the actual product review, we review all the product, not just the