insert is directed at physicians or consumers, because I don't think it can satisfy both needs.

My own bias would be that this is for the prescriber, and it is the prescriber's role to sit in consultation with the patient and translate the information as necessary, which means the prescriber has to be able to understand the information.

I'm a little wary also, as someone else has mentioned, about the management section. It seems to me the guidance for management ought to flow from the risk assessment information, because that is the information that the prescriber and patient need to take into account, but it may not result in the same management decision.

The example of Leural is kind of interesting, because in the pregnancy statement clinical management says in the second sentence, "women who are considering pregnancy should be advised to consider alternative treatments for asthma maintenance when feasible."

Well, you know, that can be interpreted any of a number of ways, but one concern from a

liability standpoint would be that physicians would shy away from the drug, and yet for a given patient, that may be the appropriate drug, all risks notwithstanding.

So I'm a little wary of the FDA sitting in judgment of a clinical decision which presumably is being made rationally. I mean, you just have to, I think, assume that at some level.

So I think that, if the risk information is given in a meaningful way, it would be possible to avoid the management recommendation which, as I said, ought to flow.

On a separate level, somewhat separate level, and others have stated it, but I would just want to reinforce it, I think it's really important that the document acknowledge ignorance right up front and, you know, take all the heat that the practitioners are going to throw at it.

Certainly, the FDA will be called cowardly for saying we don't know, but the truth is the truth. I think that it also ought to acknowledge where there's controversy.

I'm not sure I disagree with you, Mike, when you were talking about the AHCPR standards, but I certainly haven't seen any assessment of conflicting epidemiologic data in humans that has used a set of standards which large numbers of experts in the field will agree on.

You know, I mean, we're certainly involved in that kind of area of inquiry, and others have had experience in it. I think that the practitioner needs to know that there may be controversies surrounding the interpretation of human data, and the agency ought to be encouraged to be up front about that.

Finally, two other points. One is the animal data. I'm further away from the table than Ken Jones, but I would tend to agree with him, and certainly, if you look at the history of human teratogenesis, the animal data aren't terribly predictive.

They may be predictive for other outcomes than teratogenesis, but when it comes to birth defects, there are very, very few animal studies which people would consider to be predictive.

I think to overstate the animal data simply because they're available would provide a disservice, either because they provide assurance or they provide evidence of risk, unless there's some good reason to believe that that information translates to the human condition. I'd be kind of wary of it.

Finally, I wonder whether it would be appropriate for the agency to consider -- I hate to use the word boilerplate, but I think physicians may not consistently look at the package insert. Enlightened consumers may not either.

It might be useful to consider sort of a baseline introductory few sentences that provides information on baseline rates of birth defects, for example, that provides a statement about the need to balance risks and benefit in a given patient.

I actually like the idea of suggesting the need for expert advice where the practitioner feels that's necessary. That kind of statement with every insert might actually prove to be quite helpful. I'll stop there.

CHAIRMAN GREENE: No, you're absolutely correct that the AHCPR hierarchy, if you will, of quality of data doesn't pertain to judging epidemiologic studies. It pertains to recommendations for patient management.

DR. MITCHELL: Yes, and certainly having seen different meta analyses of the same subject or even systematic reviews, which I would prefer, different observers come to different conclusions, and all of them can argue that they're correct.

CHAIRMAN GREENE: Absolutely. Reasonable persons may differ.

MS. CONOVER: I just wanted to address briefly the issue of boilerplate, because I think that some of that will be needed.

At our teratogen project we've tried doing what we call the disclaimer in two ways, and almost all teratogen projects use some kind of disclaimer, including reminding people of their three percent background risk and also that there's never complete data and that data changes, and they need to re-consult us for additional data periodically.

We've done it both in a paragraph that kind of comes after the introduction, you know, stating the background of the particular problem we've been consulted on, and we've tried inserting it within a paragraph.

I have to say that, although it's easier to put it in the second paragraph, to kind of lump it altogether, I'm not sure how often it gets read or understood in that format. In fact, we've had more success when we'll say something like Deprocote has a two to six percent risk for neural tube defects; this can be compared to the background population risk of, you know, .6 percent or whatever you choose to use.

I think that when it's embedded in that way, compared directly, it's harder to do, but I think it's read and understood more effectively.

CHAIRMAN GREENE: I think what I'd like to do is -- and that's a good segue. The discussion to this point has really addressed, I think, reasonably well the first three questions.

What I'd like to do now is to focus attention on question 4, which is with respect to

whether information should be quantitative and numeric in some way or qualitative using descriptors for risk.

In the question it specifically chooses the example of risk ratios, and I would plea specifically that risk ratios not be used, because two or three or ten times a risk ratio, if it's a very small number to begin with, is still a very small number.

For example, an increased risk for neural tube defects with Valproic acid of 10, if you start with a background rate of one in 1,000 and you raise that to one in 100, one in 100 to most patients sounds like a relatively small risk; whereas, if you tell them you have a tenfold increase in risk, that sounds very daunting.

So I think that, if we're going to use numbers, that they be absolute risks and not relative risks. Then whether we also need some sort of a qualitative description of risk, I'll throw open to the committee for discussion.

Patrick?

DR. WIER: I'd like to start with the

situation where you have a new chemical entity and there is no clinical data. I'd like to start with the situation where you only have animal data, and try to explain what I think state of the art is in terms of making a prediction of risk.

I think this is relevant, because when we saw the presentation earlier, what the summary statement distilled down to was no concern or significant level of concern. I made the comment, well, we're always concerned; what can we say?

Here's the way that I would sum it up, is that when you look at animal studies and we do current state of the art evaluation with regard to biological plausibility and exposure level in animals relative to the clinic, we can make statements that include there is no a predicted hazard under the clinical exposure condition. That's a definitive statement that can be supported scientifically.

There are things at the other extreme where we know, based on biological plausibility such as the role of the therapeutic target in development, the exposure levels being low, being consistent with

the pharmacologically active exposures, where we see abnormalities in development, that we can make the other clear statement that it predicts. The animal studies predict with high probability a hazard relevant to the clinical exposure condition.

Now where the state of the science has not yet evolved is in that middle ground. I think what can be used in a summary statement at a sort of semi-quantitative level is to say that the hazard from the animal studies is a potential risk or a possible risk or is considered potentially relevant.

I think that's the state of the art today with the animal studies.

CHAIRMAN GREENE: Yes, please?

DR. O'LOUGHLIN: As far as the qualitative wording, at least from a patient point of view -- I mean high, medium and low can be very anxious to individuals, because people have different definitions. I mean, you know, I may think high is not that bad, because I've looked at an integration tool, and I understand that it's weighted, and I understand, you know, that there's thresholds and

whatever.

So when it comes out high, I look at it, and I say, well, that might not be so bad. But somebody who might not understand how that data was derived to get a high level may be extremely anxious and not even want to discuss a drug.

So I think it's up to the labeler at that point on the high, medium and low. That's a real difficult thing for patients to understand.

CHAIRMAN GREENE: This is a mathematician talking here.

DR. O'LOUGHLIN: Yes.

CHAIRMAN GREENE: Yes, Jim?

DR. LEMONS: When it's known -- You know, Francois had posed the European, I think, definition where they use the scarce, uncommon, common, etcetera, and equated that to a definitive number, which I thought was helpful; because I know it's been suggested by some of the lay groups that some type of qualitative and quantitative might be useful, but they probably should be identified in a boilerplate. It may be one other thing that could be put into the

boilerplate that Allen was suggesting, when that's known.

MS. CONOVER: This is one of those areas I was alluding to in genetic counseling where they look at counseling men versus women. There's at least beginning to be, and certainly a lot of discussion in genetic counselors, that our male clients respond better to numbers like percentages or we'll use ratios one and 20 or whatever. We'll present it different ways, and that women often see things more absolute, not very likely, very likely -- you know, those kinds of areas where you're using phrases instead.

Again, of course, you have to define what those phrases mean, and that's the hard part, but it might be something to take into account.

CHAIRMAN GREENE: Other comments? I'd like to then direct your attention to question number 5, which is with respect to the goals for the Discussion of the Data subsection, and how should information be selected for inclusion in that subsection.

Ken, should they not even mention animal

studies in that section?

DR. KWEDER: Can we go back for one second, Mike?

CHAIRMAN GREENE: Yes.

DR. KWEDER: One of the things that you haven't touched on with regard to the quantitative descriptions of risk that was touched on earlier this morning was the issue of competence intervals.

Some people have suggested that -- this is particularly the case when we have human data, not animal data, that we describe things in terms of, well, we know that the risk may be somewhere between here and here. Even though it's a broad spread, this is the level of certainty that we have.

It's probably higher than one in 1,000, but not as much as one in 100, something like that. Is that kind of quantitative description -- does that have a role here? We've done it in labels in regard to other safety data. I'm trying to put some context to the numbers and what magnitude of risk that's being discussed, and so I'd just like to hear any comments that you have on that.

CHAIRMAN GREENE: My immediate response is that something like that is essential, because it conveys to the reader the quantity of data available to address the issue. Obviously, the less data available, the wider your confidence intervals, the less stable your point estimate of risk.

So I think something like that, as I said when handling zero numerators, this pertains elsewhere, too.

DR. MITCHELL: Could I interject?

CHAIRMAN GREENE: Yes, Allen?

DR. MITCHELL: I think that there's a serious difference between safety data that comes out of either preclinical or post marketing randomized trials and epidemiologic data that are likely to bear on the question of birth defects.

That has to do with the validity of the study. I know I'm repeating a theme here, but I really think it needs to have some focus.

It's very easy and sort of reassuring to say, well, let's look at all the studies that have been done in humans and describe the risk magnitudes

that those studies have identified, but in fact, if there's one good study and six bad studies, I think most people would argue, under the assumption they could agree on what's good and what's bad, that it's only worth presenting the data from the good study.

It seems to me that the preliminary activity and the more difficult activity that falls on whoever is preparing these documents is to make some judgment about which studies are worth including in that assessment of magnitude of risk.

CHAIRMAN GREENE: I think this does address the next question, which we had just asked, which was what data should go into the subsection.

DR. JONES: Mike, could we just continue on this particular issue for just a minute?

CHAIRMAN GREENE: Yes, please.

DR. JONES: I'd just like to respond, I think, to what you were saying, Sandi. Were you creating a hypothetical situation in which you said one in 1,000 -- less than one in 1,000 versus greater than one in 1,000 or were you basing that on numbers?

DR. KWEDER: Those are just hypotheticals.

I think that sometimes -- What some clinicians have said to me when we've talked about labels, they'll say, you know what, here's what I want to know; I want to know if this is thalidomide, and tell me if -- is that the kind of risk we're talking about here when you say that there's risk? Is that what you mean or do you mean Valproic acid and neural tube defects?

So I'm trying to get at the challenge of helping people understand what magnitude of risk is being dealt with, and what kinds of ways can we choose to describe that?

DR. JONES: Well, I -- Obviously, I agree. I think that's incredibly important. Unfortunately, I'm not sure to assign a number, one in 1,000 -- I mean, that's pretty artificial. I mean, you really are making something up.

What we do in TERIS in a situation like this, we have a boilerplate statement that we make which could be something like "a very small risk cannot be excluded, but a high risk of general anomalies in children of women treated with Blank drug during pregnancy is unlikely."

I mean, I think to say greater than 1,000 versus less than 1,000 is really -- I mean --

DR. KWEDER: Okay. That's helpful. Thanks.

DR. ANDREWS: This is an issue we've struggled with for many years in the various pregnancy registries that we have developed, and we've struggled with trying to communicate accurately what we've seen.

Indeed, we follow that model precisely, summarizing our data with the point estimate and confidence intervals, compared to the background rate. There, I would say one has to be extremely careful what you're comparing it to.

So you couldn't just take that in the abstract and say, well, we found a risk of 3.2 percent. That needs to be compared with data from the general population or the appropriate comparison population using the same kind of detection method. Otherwise, one could easily draw the wrong conclusion.

CHAIRMAN GREENE: Yes, please?

DR. CHONG: I was going to address the issue of quantitative versus qualitative data being

presented in the labeling.

I believe from my lessons from my eight-year-old son when I went to visit the school he was going to, they said people learn things or hear things in different fashions. I think this repeats something that someone said. Whether or not there's a gender bias -- I'm not going to get into that, but people do hear things and see things differently.

Their lesson was that in a good school, a good teacher will present the same material in a way that may be six different ways of learning data can be touched on at least once during that day.

Maybe we don't have room for this in the label, but the lesson is probably the same, that we need to present information in formats for different people.

The other thing I would say is like I've just gone through a month of teaching evidence based medicine. What I found during that time is who the average clinician is or the average consumer is, that they don't necessarily understand numbers, things like relative risk and absolute risk, as well as people who

are in the academic field who are doing research or doing publications, and that there is a role for us to try to address them in labeling.

DR. ROSENE-MONTELLA: I just wanted to add one more concern that we've maybe not touched upon again this afternoon. That is that whether we have an extensive clinical recommendation portion or not, that we have to continuously be vigilant about the risk of not treating maternal illness.

We counsel so many -- I see patients every day with asthma exacerbations, with uncontrolled hyperthyroidism, with uncontrolled horrible hypertension -- it goes on and on and on -- from withdrawal of meds because of concern about the safety of meds.

So I would like to see us be able to address that risk as well, and that's a good part of a risk/benefit analysis of taking a drug. I don't know if that belongs in the summary risk section or in the clinical management section, but I really don't want us to forget it.

DR. DATTEL: Just a comment about that.

I agree with you, and I think it almost seems to me, in looking at all the information that's been presented, that we almost need a statement at the very beginning: Pregnancy risk unknown, or pregnancy risk -- so that the person who reads that first sentence then goes down to read exactly what we're talking about here.

It seems like the vast majority of clinicians, as has been alluded to, want something up front to tell them whether they need to read any further. You know, Tylenol, ampicillin, maybe they don't need to read any further, but if some of these other drugs they are less familiar with, like Dr. Briggs alluded to, that they don't have any information about, they need to know that this is clearly a risky drug. They need to read about it. This is something that nobody knows anything about, they need to read about that.

Then they get into this area where you talk about following drug levels of tricyclics, because it's been shown in pregnancy they do this, or the risk of not treating thyroid disease and then

having thyroid storm -- you know, that type of an issue.

It seems like something has to be stated up front to make someone go down to -- this gets into writing for the general non-academicians to make them go down to the next level.

MS. CONOVER: Let me just say in terms of the risk of the condition, this is another one of our little boilerplate areas where, like if you have asthma, you talk about the asthma drugs and then you say, of course, it needs to be considered that asthma presents risks to both the mother and -- you know, uncontrolled asthma presents risks to both the mother and the fetus.

I mean, it doesn't even have to be incredibly detailed. It's just reminding them that it has to go into the equation.

DR. ROSENE-MONTELLA: Our boilerplate statement about that is a quote from one of our colleagues which was just always that fetal wellbeing depends on maternal wellbeing.

DR. KWEDER: I'm wondering if I could ask

a question. One of the things that I'm hearing is that -- at least some general consensus, that a statement about the risk is probably really the key here, and there's some level of discomfort about active -- getting active clinical management advice, and that perhaps what we ought to be thinking is more in terms of clinical considerations that might address some of these contextual issues like risk of no treatment, those kinds of things. Is that what I'm hearing?

MS. CONOVER: Well, for one thing, considerations is a nicer phrase than management, and it reflects that more in terms of what we're talking about.

DR. LEMONS: That is really important. Again, I can think of many cases where I think it would be very, very difficult to include all that's necessary. One is assuming that it's being used, for example, for the approved indication rather than off-label use, which is -- So how do you encompass the -- I think it would be impossible to state that.

To me, that's part of what has to occur

between the physician and the patient. Given that we can again identify risks based upon adequate data or just up front, as Allen had said, make sure that we confess when we don't have sufficient data or if risks are unknown.

DR. ANDREWS: To reiterate a point that's been made a couple of times, I think clinical considerations is the right term, and I think it should follow from the summary of risk, and it should derive from the data.

DR. DeGEORGE: I'd just like clarification. So what you're really -- What we are saying is that we should have this summary risk statement, some form thereof, first. That would follow by a clinical considerations statement so that the clinicians would have to have read both those parts rather than just read the clinical considerations statement.

Then that might be followed by some level of data. We're really talking about a reorganization and maybe a somewhat backing off in terms of the directiveness in terms of clinical management as

opposed to clinical considerations.

CHAIRMAN GREENE: I see a lot of nodding of heads. So I think you've --

Why don't we move on then to the last three questions regarding -- Pat, yes?

DR. WIER: I just had another comment on question 5, and it's to -- Maybe this is my one chance to try to remove some of the enigma of animal teratology data, and maybe even overcome some antiquated prejudices about animal data, but I don't know if I can go that far.

Anyway, this comment is relevant in the context of the suggested subheadings for the discussion of the data. Certainly, these endpoints of the studies are important to consider and focus on when you're at the level of interpreting the individual experiments. But if you ask me how I might summarize animal information at this level of risk communication, I wouldn't take that level of detail.

In fact, I would even suggest that this is part of the problem that clinical colleagues have in understanding what we're trying to say.

Instead, the key things to take and distill out of animal data at this level are, first, hazard characterization. Make sure you understand the nature of the hazard and the conditions under which it's produced, including dose response information.

The second subheader is exposure assessment. You have to understand the level of systemic exposure in these animals relative to the clinic.

The third are biomarkers, and biomarkers are not extensively huge, yes, but I think they are really going to be the future of making the bridge between animal studies and clinical studies.

Just to give you an example, it may be fine for me to say that when you reach a certain systemic plasma exposure, you enter a range where there is a probability of a certain adverse outcome in pregnancy, but you say, but we don't have clinical pharmacokinetic data in that patient.

On the other hand, we may know that at the same time in that level of exposure, you see changes in clinical chemistry parameters or there may be

clinical signs of toxicity.

A good example of application of biomarkers is caffeine. Caffeine produces congenital malformations in rats. It produces ectrodactyly or absence of one or more digits. This is not widely regarded as a significant clinical teratogen.

One of the reasons is caffeine is a self-regulating teratogen. The exposure levels in rats that are necessary to produce this malformation would exceed the levels that produce clinical toxicity in most people.

So there is a biomarker for you. Are you seeing these clinical signs of toxicity? I think, by translating the animal information away from these technical terms that we feel so comfortable with in the laboratory and in terms of hazard characterization, exposure comparison and biomarkers, I think that's where we can maybe make a bigger difference.

CHAIRMAN GREENE: I think that you're -- Again, this is another way of rephrasing the notion of dose ratio. At the dose that we normally use caffeine

in humans, you don't see any effects in animals.

DR. WIER: We're on the same page, Mike. It's just that I'm giving you a little bit more state of the art on this.

DR. JONES: Well, listen. We really appreciate the state of the art. I agree with you completely, and I think that, if you could do that, that would be spectacular. I think that, if you could do that, we would -- it would be incredibly useful to us, and we could translate that to our patients as we talk to them. So, agreed.

DR. WISNER: I would like to ask a question and make sure I understand the clinical application of what you just said.

Let's say we had human data about the outcomes for structural alterations, dysmorphology, embryo/fetal death and growth retardation, but we had none for a specific agent on neurodevelopmental toxicity.

If we summarize the data for the first three outcomes for humans and said, well, we have no outcome data for neurodevelopmental toxicities in

humans, let's look to the animal data. Is that what you were saying could be done, so that at least there is some information in that particular subheading, or did I miss something?

DR. WIER: Well, again, I'm not suggesting that you do it by effect. I'm suggesting that you consider all the hazards that you've identified in the animal studies. That's your starting point, and that you consider the characterization of the hazard, the exposure comparison and the biomarkers that are relevant to the risk assessment.

Now you would do this for all the hazards that you've identified in the animal studies. It may be that at some point that this information becomes eclipsed by clinical experience, and yet some is not. I think that's the lasting value of animal studies, is that it's unlikely that you will have adequate clinical data on all the different endpoints -- and I want to emphasize the extent and range of functional endpoints that are conducted in some cases that are unlikely to be assessed to an adequate degree in the clinic, in many cases.

CHAIRMAN GREENE: Okay. Then I think we'll try again to move on to the last three questions there with respect to risk communication.

Let's see. In the setting where there is little known about risk, how should we communicate this? I think Allen Mitchell stated it well. I think we just have to admit our ignorance and not try to apologize for it.

We've touched upon what do we do in the absence of human data. Patrick, I think, has elucidated that.

DR. JONES: But, Mike --

CHAIRMAN GREENE: Yes, please.

DR. JONES: I think there's a variable extent about data that we don't really know about. For example, maybe we have animal -- some animal data that suggests that there's a problem, and maybe we have -- Well, let's say we have an animal data that suggests that there's no problem, and then we have some case reports that suggest there is no problem, and we have a couple of small observational studies that involve 35 and 55 patients each that show that

there is no problem.

Now in that case, we've got animal data and we've got a little bit of human data that suggest that there is not a problem, as opposed to a drug for which we have no animal data and we have no human data.

I think that they are two separate situations that we need to make some distinction. You know, to say we don't have any data here, and we're mea culpa, that's fine. I think we should be doing that as well, but I think we should be making a distinction somehow between the two.

TERIS does, in fact, address this issue. We use something called the Hansen U, which is for Jim Hansen, for those of you who know who that is, and it's when the risk is undetermined and the quality of the data is really limited or none.

In that case, we use this Hansen U which I've already read to you. If it's strong, we say a very small risk cannot be excluded, but a high risk of congenital anomalies in children of women treated with Blank Drug during pregnancy is unlikely.

Then we have a lesser statement in which we say a small risk cannot be excluded, but a high risk of congenital anomalies in children of women treated with Blank Drug during pregnancy is unlikely.

So we sort of have two categories there, but it seems to me that the situation that I just gave you merits that kind of a statement, as opposed to there's absolutely no data, we have no idea whether the drug is, in fact, a problem or not.

We have a little data. It's not great data, but we have some data.

CHAIRMAN GREENE: I think that it would be clear to distinguish between truly no data and a limited amount of data which isn't adequate to meet everybody's needs.

Yes, please?

DR. HAMMOND: I have essentially a question. That is, is there a place for using information about other drugs in the same class for which we have more experience?

DR. DeGEORGE: Perhaps we should have actually had this meeting after we had the meeting

next month or at the end of the month, because when we go through how we're going to analyze the data, which is another public meeting, a lot of this has been brought and discussed.

In fact, we have this issue about -- I think Dr. Morse showed class information. That means you have human data on the class, either positive or negative, that either suggests that there's a potential problem for this drug, even though no one has identified for this drug, even though it's tested adequately in animal studies or that you know that, even though they're positive in animal studies, you have adequate human data that says we never have a problem with this class of drugs, even though the animals always show it.

We intend to feed that into the system about the whole dataset, which would be that -- Part of that information would be in the data discussion.

DR. MITCHELL: Could I jump in here?

CHAIRMAN GREENE: Yes, please.

DR. MITCHELL: I'm not a toxicologist, by a long shot, and I suspect that there are indeed valid

class analogies for some of the toxicologic effects of medications, but I would urge real caution about making assumptions, as the agency does, I think, by requirement, about what I call class action teratogenesis, the assumption being that if one member of a class is teratogenic or not teratogenic, then other members of the same class have either similar effects or highly likely to have similar effects.

The classic example where that is not true is thalidomide and glutethimide, glutethimide being the old Dorden sleeping pill. They are both gluteramides. They are both members of the same drug class. One is clearly an extremely potent teratogen, and the other is not.

So I really worry when there's either data that suggests no effect of a given member of the class, and people are quick to say, well, then other members are probably equally safe, or vice versa.

CHAIRMAN GREENE: Well, Allen, I guess I would press you on that and ask whether you think it's better when a new drug is introduced in a class of compounds to just throw up your hands and say we don't

know anything or to at least provide by analogy some suggestion as to whether there may or may not be a problem.

DR. MITCHELL: I -- For a couple of reasons, the thalidomide example being one where glutethimide would have been painted with the same brush under that assumption. Similarly, if you look at another example, which is Altretnate, a retinoid, a short acting retinoid that is clearly related to Acitretin, a recent publication of a number of perspectively identified pregnancies did not identify any increased risk for this drug, and yet by class labeling there would have been great concern that this is another acutane.

So I can't say that I would come down irrevocably in one direction or another, but I have much more comfort when we're talking about the toxic effects or physiologic effects of the drug class, because then we're talking about the mechanism of action of the drug.

What we are dealing with in teratogenesis is an unknown effect of the drug, in the sense that we

don't know what component of the molecule is responsible for teratogenesis. You know, again, I worry a great deal.

At a minimum, I would think that one would need to be careful if one used the class labeling for teratogenesis in explaining to the reader that it's not necessarily predictive of teratogenesis, in which case I would argue why bother putting it in.

So I think I would prefer -- Unless six members of the class share a teratogenic or even two share a teratogenic similarity, I would be wary about labeling them all equivalent, particularly when it comes to safety, statements about safety.

DR. DeGEORGE: I didn't want to leave the impression that that was the final labeling in terms of this one is a -- this member is of the same member of a class and, therefore, the final conclusion is it is a teratogen.

DR. MITCHELL: Oh, no. I'm sorry, I wasn't speaking in response to what you were saying in detail. It's just that I've heard from others and, in fact, if you look at the labeling of the

benzodiazepines or a whole variety of classes, the class -- sort of the class action teratogenesis theme is carried out, and I have concerns about that.

I mean, I agree that it can be done much more carefully, but there's a general perception that, since they share toxicities oftentimes, that they are, therefore, likely to share teratogenesis or lack of it.

MS. CONOVER: But, remember, we're not just looking at malformations. So one of the things classes do tell us is kind of an educated guess about, say, problems with newborn adaptation or some other issue on the fetus in pregnancy.

DR. MITCHELL; Oh, absolutely, and I tried to be very clear that I was restricting my comments to teratogenesis, which presumably is a very different mechanism.

DR. WISNER: I would like to ask our animal teratologists for some information about this, because it would seem to me that our animal researchers would have a lot of advice about how different drugs in the same class affect animals.

DR. WIER: There are examples in both extremes. There are examples of compounds where the developmental toxicity relates to the action of the drug on the therapeutic target; for example, ACE inhibitors.

We understand a little bit about the role of angiotens in converting enzyme in Angiotensin II, maintaining renal profusion in the fetal kidney and how that relates to fetal pathologies in the kidney. And it's very difficult then, given that, to design an ACE inhibitor that's not going to cause that fetal pathology.

So in that case, you know, you're on very strong ground when you make extrapolations across the class.

Now there are other cases where the development toxicity might relate to a secondary action of the compound, and the compounds within the class may not all have equal specificity. The intended target may be one subtype of a receptor, and there may be another subtype of receptor that could be mechanistically related to a toxicity.

Your drug might have selectivity for the intended receptor. My drug may have less specificity. In that case I would hesitate to make that extrapolation.

So the answer to your question is it depends on having that bit of mechanistic information to do it confidently.

DR. ROSENE-MONTELLA: There was just another point that I'm thinking that we haven't discussed. As I listened to everybody talk about drugs, we're talking about a drug for a dermatologic condition in the same breath as we're talking about a drug that may be treating a malignancy or a life threatening condition.

So I think somehow, as part of a risk assessment, you also have to think about the necessity of the drug. We treat all kinds of symptoms for no reason during pregnancy, and on the other hand, we withhold treatment for very critical medical illness based on our fear about an unknown effect of a drug.

So we somehow have to balance which drugs are necessary and start from there. I don't know if

that's our job or the FDA's job as you figure out how to classify drugs, because to some extent, that's a clinician's responsibility. But drugs -- We like to teach our residents even that drugs aren't safe or not safe. They are indicated or not indicated.

I'd like to see us thinking in that framework as well.

CHAIRMAN GREENE: I would guess that the FDA wouldn't want to get involved in making those kinds of drug judgments about indicated or not indicated. That is for the patient/physician relationship.

DR. KWEDER: We've done it -- I mean, certainly, we've done it to date with Category X for the most part. I think there are 20-something of those products.

We have, for the most part, tried to stay away from making pronouncements, but some of these things are the kind of things that one would -- I could envision at least acknowledging somehow in a clinical considerations context, particularly for products that have more than one approved indication,

some of the antifungals, for instance, that are used to treat onycholysis compared -- onychomycosis compared to a systemic fungal infection -- very different risk -- you know, same risk. Same risk, very different benefit. So very different thinking on the part of the clinician.

This is tough, I think, you know, and we have our own internal discussions of how to deal with what we've been calling the clinical management statement. We recognize the burden of not crossing lines of interfering with the judgment of the patient and the practitioner.

They are hard, and some of the questions that we're asking you get right to that. Where is the line? Help us a little bit with where is the line. But there may be situations, Karen, I think, where it is incumbent upon us to say something, and we recognize that. We've done it for acne with Acutane.

DR. LEMONS: Those are all excellent points, and I come back to Alan's suggestion of a boilerplate where principles that may guide decision making might be identified, because it's so hard to be

specific in any situation or in enough situations to be helpful to the clinician, but the principles are very important.

MS. CONOVER: We have a boilerplate phrase that says something about a decision about whether to use the medication would be dependent on the severity of the maternal condition, which sort of takes that into account, makes them think about that.

CHAIRMAN GREENE: Well, Dr. Kweder, have we given you sufficient guidance?

DR. KWEDER: Yes. I guess it would help me -- It would help us, I think, if you could specifically -- if anyone on the committee felt like at this late hour they could specifically address question 7.

How can uncertainty associated with the predictive value of the animal studies, particularly in the absence of human data, best be communicated?

Maybe Pat Wier's comments really spoke to that. But can anyone else comment?

DR. WIER: Just to add one thing to that, sometimes this comes up. People ask you about, you

know, the uncertainty, and that puts you at a disadvantage when you're trying to explain what you do have.

There's a way to turn it around and, instead of talk about uncertainty, you talk about the weight of evidence you have. That can be a more successful approach to take and say, you know, in a relative sense, we're dealing in this case with a limited weight of evidence, in another case an extensive weight of evidence.

There's always uncertainty, but you're putting it into that perspective of we're more competent in cases where we have a greater weight of evidence, rather than trying to quantify varying degrees of uncertainty.

MS. CONOVER: You know, the problem with that is we virtually never see that in the animal data we look at. I don't know if people don't want to put their neck on the line or what. I can't think of a study where someone actually came out and weighed their certainty of how the animal data had relevance to humans.

DR. WIER: Just to make a plug for the integrated data analysis scheme, the so called Wedge, I think what's really great about what the FDA has produced there is that's really a nicely formulated weight of evidence approach to data evaluation. I think we ought to encourage more of this type of thinking.

DR. KWEDER: Question 8 -- We've had many comments made to us in many forms about, you know, people kind of cringe at some of the language in labels, and talking about how some of the words that are used carry great emotional weight and connotation, and simply by their use -- like no one reads the rest of it.

I was wondering if you could maybe -- I don't want to plant any seeds, but is that something that the panel recognizes as a challenge that we have to deal with, and what are some of those?

I guess I also -- like "caution" is one of them. What does caution mean? Placental barrier is another one that people have used. Beth, you probably could speak to this a fair amount as a genetics

counselor.

MS. CONOVER: You know, for some reason, the statement is often made that it crosses the placenta in rats. It makes my patients terribly anxious. I can explain to them that, of course, we kind of think everything crosses a placenta. I mean, until proven otherwise, we worry about it, and that that shouldn't alarm them. But for whatever reason, it doesn't provide a lot of help to me in making the risk assessment, and it alarms my patients, and actually their providers.

So I think that could be deleted.

DR. O'LOUGHLIN: I think you probably want to just stick to stating facts instead of like interpretation type words like caution, you know, low, high, stuff like that. I mean, if it's factual based, I think people can really understand that better than something that's been interpreted by even a large group of people that put it down.

I mean, it's up to the interpreters, and that's not every provider or patient that's out there.

CHAIRMAN GREENE: Other thoughts? Yes?

DR. ANDREWS: As I said before but worth restating, that the word concern is less helpful than to state the facts, state the data, state what the known risk is.

CHAIRMAN GREENE: One other word that I find laypersons tend to misinterpret is the word probability. When they hear probability, they think we mean it is likely, whereas we interpret probability as sort of a neutral. The probability could be extremely small, but there's still a probability.

So I think that the word probability is problematic.

MS. CONOVER: And practically all the phrases used in the animal things like delayed ossification, you know, are just terribly alarming to patients and providers, and it's almost to the point where you can't use the phrasing.

One of the things we learn in genetics is we don't use the word teratogenesis. I mean, we have lingo for everything, but when we talk to patients and providers, we mostly take it -- you know, we delete it, because it suggests alarm when you're not

necessarily trying to phrase that.

DR. KWEDER: So what would you use instead?

MS. CONOVER: Well, now as a provider actually -- put that hat on -- delayed ossification is of less interest to me than what does that mean. Do you know what I mean? I mean, I guess if you use the phrase, you always have to explain it. But I had a situation recently where there was an animal study suggesting that it looked like it was related to toxicity, and they had an ultrasound where the fetus was missing an arm, and they were making a direct link because of this.

I think, you know, they just don't understand what the animal data is telling them, but they were alarmed. The patient was alarmed. I mean, everyone was alarmed by the phrase.

So I think they are very poorly understood. I think long words that sound very technical -- and that's not talking down to patients and not talking down to providers. I just think it's true.

CHAIRMAN GREENE: But that may be a good example when delayed ossification is an observation in either animal or human data, that delayed ossification does not mean absence of a limb. That's where it may be inevitable that laypersons are going to need professionals to help interpret the information.

DR. WISNER: I think before, too, when I raised the issue about the subheadings, we will have exactly this problem with the current way the subheadings are titled.

I would again press for operational definitions. For example, dysmorphogenesis as a subheading or functional toxicities have a kind of negative valence to them that we might want to think through.

My main problem with the verbiage that occurred in some of the labeling really had to do with statements like the risk for injury to the fetus must be balanced against the risk of permanent injury or harm to the mother, those kinds of very powerful statements that patients read that might cause them to abruptly discontinue a medication that could be very

important for them to be taking.

CHAIRMAN GREENE: Other comments? Dr. Kweder?

DR. KWEDER: I could keep you here until tomorrow, but I won't. I would just like to thank all of you for your thoughts and your participation.

I think what we'll do is -- I've certainly taken copious notes. We have a transcript of this. I feel that the message we've gotten from you -- much of it relates to sort of tweaking the general idea of what we have and fine tuning how we would facilitate its implementation in a way that will allow information to be put out that's meaningful and useful for clinicians and possibly patients.

I can't promise you that we will take every suggestion you've made, because many of you haven't agreed. So we'll have to take all of that into consideration and see what we can come up with that's workable.

We will probably develop more models and take them out for focus testing based on your comments. We think that that is a subjective tool,

but it does -- you know, it's pretty real life.

I would like to tell you that we may reconvene this subcommittee in the future to address more detailed data assessment questions and even possibly help us with difficult cases that we are encountering at the agency.

So I want to thank you all so much for making the trip here. We really appreciate your time and the obvious great deal of thought that you've put into this.

CHAIRMAN GREENE: Thank you. Yes?

DR. WISNER: Can I ask a final question? We got this wonderful handout about the FDA videos, and I'm assuming that the video tape of this session would be -- No? But I do have a question about whether -- I understand the copyright restrictions, but I want to clarify that the FDA has no other specific restrictions on how this might be used. We can show it for educational purposes?

DR. KWEDER: Kimberly, can you address that?

MS. TOPPER: The FDA has absolutely

nothing to do with the gentlemen who come and do the video taping for us. They do it as a business. They are allowed to put fliers out. If you are interested in purchasing it, be my guest. You can use it however you want. Please be nice, though.

DR. WISNER: And I also just want to say I thought that the presentations today were very excellent, and I was frankly not looking forward to coming to yet another conference, but this really was a very stimulating conference.

CHAIRMAN GREENE: Agreed. Thank you all.

(Whereupon, the foregoing matter went off the record at 4:16 p.m.)

C E R T I F I C A T E

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Before: PREGNANCY LABELING SUBCOMMITTEE

Date: JUNE 3, 1999

Place: SILVER SPRING, MARYLAND

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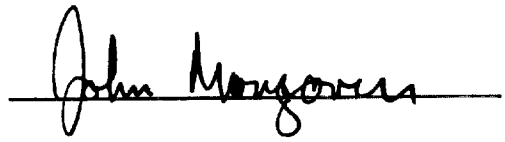

Look-See Concordance Report

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UNIQUE WORDS: **4,152**
TOTAL OCCURANCES: **21,213**
NOISE WORDS: **385**
TOTAL WORDS IN FILE: **59,985**

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SINGLE FILE CONCORDANCE

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CASE SENSITIVE

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NOISE WORD LIST(S): **NOISE.NOI**

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