U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE

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PREGNANCY LABELING SUBCOMMITTEE

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THURSDAY

JUNE 3, 1999

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The Subcommittee met in the Kennedy Ballroom in the Holiday Inn-Silver Spring, 8777 Georgia Avenue, Silver Spring, Maryland, at 8:00 a.m., Michael Greene, M.D., Chairman, presiding.

PRESENT:

MICHAEL GREENE, M.D.	Chairman
ELIZABETH B. ANDREWS, Ph.D., MPH	Member
GERALD B. BRIGGS, Pharm.	Member
CYNTHIA M. CHONG, M.D.	Member
ELIZABETH ANN CONOVER, M.S.	Member
JANET DARDEN GRAGAN, M.D.	Member
BONNIE J. DATTEL, M.D.	Member
MARY G. HAMMOND, M.D.	Member
KEN LYONS JONES, M.D.	Member
JAMES A. LYONS, M.D.	Member
ALLEN MITCHELL, M.D. (by telephone)	Member

PRESENT:

VICTORIA O'LOUGHLIN, Ph.D.	Patient Representative
KAREN ROSENE-MONTELLA, M.D.	Member
JULIA R. SCOTT, R.N.	Consumer Representative
ALAN TAYLOR, Ph.D.	Member
PATRICK WIER, Ph.D.	Member
KATHERINE L. WISNER, M.D.	Member
KIMBERLY LITTLETON-TOPPER, M.D.	Executive Secretary

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:05 a.m.)

CHAIRMAN GREENE: Good morning. Thank you, everyone, for coming. My name is Mike Greene. I'm from Massachusetts General Hospital in Boston, and I've been asked to chair the committee.

I'd like to officially bring the committee to order and ask Kimberly Topper, who is our staff support person, to help me get the meeting started, please.

MS. TOPPER: I'm going to read the conflict of interest statement.

This following announcement addresses the issues of conflict of interest with regard to this meeting and is made as part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that, since the issues to be discussed by the committee will not have a unique impact on any particular firm or product but rather may have widespread implications to

all similar products. in accordance with 18 U.S.C. 208(b)(3) general matter waivers have been granted for all of today's meeting.

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

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

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

Because this is the first time this committee has met, and many of you have never sat on an advisory committee, I'd like to remind you that you need to speak directly into the microphones. This is being recorded. We have a verbatim transcript, and if

you don't, I'll yell. Please speak into the mike. So I would appreciate your attention to that.

Also, in order to have everyone not speaking over one another, if you will indicate to the Chair that you would like to speak by raising your hand or some other method, he will call on your. That way, we'll have orderly and we'll have a good transcript. Thank you.

CHAIRMAN GREENE: Thank you. Next, I would like to go around the table and ask all of the members of the committee to formally identify themselves, please. So I'll start.

My name is Mike Green. I am an obstetrician/gynecologist at the Massachusetts General Hospital in Boston.

MS. CONOVER: My name is Beth Conover. I'm a genetic counselor, and I run Teratogen Information Service in Omaha, Nebraska.

DR. DATTEL: Bonnie Dattel, Professor of OB/GYN, maternal/fetal medicine, Eastern Virginia Medical School.

DR. WIER: My name is Patrick Wier. I'm

a preclinical scientist in reproductive toxicology for SmithKline Beecham Pharmaceuticals.

DR. LEMONS: I'm Jim Lemons. I'm a professor of pediatrics and direct the newborn intensive care programs at Indiana University Medical Center.

DR. ROSENE-MONTELLA: I'm Karen Rosene-Montella. I'm an internal medicine doctor who is running a medicine program at a large women's hospital, and we have a fellowship in medical problems in pregnancy.

DR. CRAGEN: I'm Jan Cragen. I'm a pediatrician epidemiologist with the Division of Birth Defects and Pediatric Genetics at CDC.

DR. KWEDER: I'm Sandra Kweder. I'm the Acting Director of the Office of Drug Evaluation for FDA. That means we actually regulate all products to treat infections, but I'm also the Co-Chair of the agency's Pregnancy Labeling Task Force.

DR. DeGEORGE: I'm Joseph DeGeorge, an Associate Director for Pharmacology and Toxicology in the Office of Review Management in the Center for Drug Evaluation Research.

DR. CHONG: I'm Cynthia Chong. I'm the Assistant Medical Director in a large municipal primary care service where we do medical consultation, including the back-up to the obstetrics department in the University.

DR. BRIGGS: I am Gerald Briggs. I'm a clinical pharmacist at Long Beach Memorial Medical Center in Long Beach, California, and Women's Hospital in obstetrics/gynecology. I'm also the author of the book, Drugs in Pregnancy and Lactation. I'm on the clinical faculty of schools of pharmacy at the University of California, San Francisco, and University of Southern California.

DR. O'LOUGHLIN: My name is Victoria O'Loughlin. I'm a mathematician with the Department of Defense for the Navy, and I'm here as a patient representative.

DR. TAYLOR: I am Alan Taylor. I'm Vice President for Drug Assessment at Gilead Sciences. I'm responsible for regulatory and toxicology at Gilead.

DR. ANDREWS: I am Elizabeth Andrews, an epidemiologist. I head the Epidemiology Group at

Glaxo Wellcome where one of our functions is to conduct observation studies of drug safety.

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

DR. WISNER: Katherine Wisner. I'm a professor of psychiatry and reproductive biology at Case Western Reserve University, and I run a clinical and research program for women with psychiatric illness who are in pregnancy or in the postpartum period.

DR. JONES: My name is Ken Jones. I am in the Department of Pediatrics at the University of California, San Diego.

CHAIRMAN GREENE: And we have one person who is participating remotely, Dr. Alan Mitchell. Alan, if you would identify yourself.

DR. MITCHELL: Sure. I'm Alan Mitchell, Professor of Pediatrics and Epidemiology, Sloan Epidemiology at Boston University.

CHAIRMAN GREENE: Thank you, everyone. I think the --

DR. KWEDER: Mike, I'd like to introduce one more person, since he's sitting in the center of the room. This is John Mahoney. He works in our office. He is our computer techno whiz, and he's going to be in charge of all of our graphics and slides today. So if you need anything, that's John.

CHAIRMAN GREENE: Thank you. I think, with the introductions complete, we're ready to move on to Dr. Lumpkin.

DR. LUMPKIN: Good morning, everybody, and welcome. My name is Murray Lumpkin. I'm the Deputy Center Director at the Center for Drug Evaluation and Research.

I have a delightful task today. I don't have to talk about the science. I don't have to do anything along those lines. My task is just to welcome you all and to particularly thank the Committee for being here.

This is a marvelous committee. I've worked with Sandy and talked with Sandy about the individuals who are on the committee, and I don't think either Janet Woodcock, our Center Director, or

I could be any happier with the caliber and the kinds of people who have agreed to come and help us with this particular issue.

I think, for those of us in the Center, this is an extremely important meeting, and I think for many of you on the Committee and many of you here in the audience, it's obviously -- it deals with an issue that's very near and dear to the hearts of many of us.

I think, before the end of the day, you guys will obviously have had a very interesting and, I hope for you, and I know for us, a very, very helpful discussion of the issues of the use of drugs in pregnancy.

I think, when we look back over this century and we start thinking about some of the very, very good things that came out of the century, one of the things that will go to the top of that list will be the tremendous health benefits that modern pharmaceuticals have brought to not only Americans but people around the world.

I think also, one of the things we have

learned this century is that drugs carry with them risks, and one of the real challenges that we have as regulators, we have as the health care community, and we have as individual patients is how do you balance those wonderful benefits that many drugs give us and the often very, very real, very, very serious risks that the drugs can carry.

Part of that challenge is how do you communicate what the benefits are, what the risks are, what we know, what we don't know, what the reality is at any given point in time. This challenge on communication, I really think, has two components, and perhaps as the discussion goes on today you can help us along those lines.

One is what is the content of what we say? What is the message that one is trying to get across? The second is what is the mechanics for doing that?

We have so many wonderful media that are available to us today to communicate. Clearly, the label is one medium, but I think all of us realize the reality of communicating to the health care community, communicating to patients, communicating to colleagues

around the world really have to involve media beyond that.

So the challenge is figuring out what the content is and what the media are that we can use to get out this message of risk and benefit, not only for the drug itself in the issue of pregnancy, but all the issues of risk and benefit involving modern pharmaceuticals.

The second challenge I think we've had as we've gone along through this century is we have continued to learn that the message is not always the same for every group. One message does not always satisfy each group.

I think, as we start looking at the many elements of our society that are affected by drugs, we've realized the message for children is different from the message for adults often. The message for the elderly is perhaps different from the very elderly.

The message for those who, for survival and quality of life, have to have a life of polypharmacy is not the same for 24-year-old healthy

males in a Phase I trial, the issue of our various ethnic groups and the physiologic differences that express themselves sometimes in the way drugs are used, the physiologic differences between men and women, the issue of lactating women, and finally the issue that's before us today, the issue of the use of drugs in women who are pregnant.

If you think about it, this is a group and this is a situation where, as a community, we probably want to know the most. We really desire-- We're talking about the next generation here. What is the effect on the mother? What is the effect on the child? But yet it's an area where we all agree, we have very, very little knowledge.

Part of what we are trying to look at here and part of our challenge with you today is to realize what we do know and what we don't know, and again the communication -- or the challenge of how to communicate that information.

I think we all realize there is a tremendous dearth of clinical information involving the use of drugs in women who are pregnant, and there

are a myriad of reasons why that is true, but the bottom lien is it is true.

The other truism is that most of our clinical decision making we often try to make looking at our experience in animals, and we do a fair amount of repro-tox work when drugs are being developed, but the question is what does that mean in human clinical practice? How do you extrapolate what we see in animal reproductive toxicity studies to the clinician, to the patient who is pregnant? What does that mean, and how do you communicate what we know there?

I think, as a regulatory agency, as a health care community, as individual patients, this issue of getting a grip on the lack of clinical information and getting a grip on what we know from animal reproductive toxicities and how we translate that into clinical decisions and individual patient decisions gets to the heart of informed consent, which is really the heart of how medicine, we believe, should be practiced in this country.

So what we have tried to do is recognize that we believe that the present way that we label

products with the pregnancy categories and these kinds of things has not done the kind of job that we wish it could do, that clearly there must be a better way forward to try to communicate what we know and what we don't know about the use of drugs in pregnant women.

So several months ago -- I guess, Sandy, now it's even over a year ago now -- we put together a pregnancy labeling task force that's co-chaired by Dr. Kweder who introduced herself a few minutes ago, and by Dr. Bern Schwetz, who is the head of FDA's Center for Toxicological Testing down in Arkansas.

So we brought both the clinical side and the pharmtox animal side together and gave them a challenge. Could I have the overheads? This is my only overhead.

Really, the challenge to this particular group involved this issue of communicating drug benefits and risks when drugs were being used in pregnancy, and one of the challenges to the group was to go out and find what are the expectations of the community; what do health care practitioners expect as far as the information is concerned; what do the

patients expect as far as the information is concerned, so we can begin to gauge whether we are or are not as a community meeting the expectations of the broader community.

The challenge was to go out and look and see what expertise is available. I think we feel very good about the expertise that we have in-house, but clearly this is not something we can do by ourselves.

There is a large body of expertise available in this country and in other countries, and the challenge was to go out and tap that. I think, as many of you know, we've tried to do this through a Part 15 public hearing that has occurred.

Obviously, the session here today is part of the challenge to this task force, to tap into the expertise that exists in the country, to help us finally at the end to find a better way forward.

I think you will be hearing from Sandy and other people on the task force at least the early drafts of a proposal of perhaps a better way to go forward to communicate what we know and what we don't know about the use of drugs in pregnancy better than

we have communicated it in the past.

So with that, I'm going to, first of all, again thank you very, very much for being here. I hope this has set some kind of context around the purpose of this meeting. I know Sandy and the other members of the group will be bringing you along and talking with you and getting feedback from you on many, many points.

I want to turn the meeting over to Dr. Kweder at this point. Let me tell you a little bit about her. She didn't quite introduce herself as fully as I would have done.

Sandy is, as she said, the Acting Director of our Office of Drug Evaluation IV, which is the office that deals and oversees the three divisions that have primary oversight for all the various antimicrobial drugs in this country, and she does have an infectious disease background.

Actually, this issue of the use of drugs in pregnancy is something that has been very near and dear to the heart of Sandy for a long time, so much so that about four years ago, I guess, now Sandy took a

two-year leave of absence from us and went to Providence and became a Fellow, did a fellowship in the program there you've heard about where people go and deal with the medical problems of pregnant women.

Obviously, this goes to the heart of the use of drugs to treat the medical problems of pregnant women. Sandy did a fellowship, a two-year fellowship. We were very, very supportive of this, because this was an area of expertise that we desperately needed in the Center. Sandy, we knew, who was a person who could get that expertise and bring it back.

I think what she's done in leading this particular task force is indeed some of the fruits of the support that we put into that. I think that's wonderful to have her here. I wanted you to know that was a little bit of her background and why a person who heads an ID office also was chosen to do this.

So with that as an introduction, Sandy, I will turn this over to you. Again, than you all for being here, and I know we're going to have a great discussion here today. Thanks very much. Sandy.

DR. KWEDER: Good morning. I want to echo

Mac's comments and thank you so much for coming.

My task for today is to really lay out the ground work and let you know about where we've been with this issue of labeling drugs for use in pregnancy, where we are now, and give you a flavor of some of the other projects that we see as future endeavors.

I think that this is not an easy topic. We recognized early on that it's not enough to just say, well, we don't like these categories anymore, we're just going to change them tomorrow. It's really a much more complex set of objectives that have to go into that and a lot of planning.

So I'm going to talk about labeling products for use in pregnancy, past, present, and new directions.

Now these are the topics that I'm going to cover today. I'm going to walk you through this, because there are some elements of my talk that maybe don't naturally flow from one to the other. So I'm going to try and give you some cues and tell you, okay, we're going to move on to the next topic.

You should have copies of my slides as well as slides of all of the speakers in the red packet in front of you. Now I would also like to mention that one of our speakers and one of the subcommittee members, Dr. Koren, called yesterday and had an emergency and couldn't come, and sends his regrets. So that's why you don't see Gideon at the table.

I'm going to first give you an introduction to labeling, because I know that most of you are new to this advisory committee process, and haven't had -- Even though we're not dealing with a single product today, I think, there's often confusion when we talk about labeling. So I'll give you Labeling 101 in a few slides.

I'll talk about the current regulations or categories, including some history of them and what we've found in working with them over the 20 years of their existence, and then the bulk of my talk is going to be directed at giving you some background on the Pregnancy Labeling Task Force that Mac Lumpkin just mentioned.

I'll spend a lot of time talking about the feedback that we've had on pregnancy labeling, and then tell you some things about other activities that we have going on in this area. Finally, I'll wind up with objectives for today's meeting.

Now I'm going to tell you, we have four major parts of the talk, and I did ask John Mahoney to give me some little transition slides with fades. So that will be your visual signal that we're changing general headings. Okay? I told him not to go too wild. Next slide, John.

This is just four definitions as a glossary. Not to insult anybody's intelligence, but lots of times at FDA, you know, we have our own lingo, and I want to make sure that we're all on the same page. I'll use these terms throughout the talk. I just want to make sure we have a baseline understanding.

First, the category system is the present system that we have of assigning pregnancy labeling, letter categories to drugs and biologics. This was established by law in 1979. It's not an option for us

to not apply it. We must, to all new drugs and biologic products. It's important to know that that system is a law.

Second is the term label. Label means different things to different people. We have food labels on Wheat Thins. The label for drugs is the official FDA approved package insert of a drug or biologic product.

I happen to have one with me for a Fluoroquinolone antibiotic. This is the thing that you get, you know, with your mugs and pens sometimes. It's in the PDR, but when I use the term label for purposes of today, and when most of the speakers do, this is what we're talking about.

Guidance documents: This is a term that may be new to many of you. It's actually sort of new to us. A guidance document is an official communication mode. FDA uses guidance documents, because Congress says that we will, to communicate information about our current thinking on a topic.

They are not regulations. They are not laws. So they're not binding, but when we have a

topic where there's a great deal of interest and we get asked a lot of questions about it or we anticipate that we will, we try to put together our current thinking as a guidance document, and I'll refer to a couple of those today.

The important thing is that they are not binding. They are not laws. We can change them.

Then finally the term Part 15 hearing: One of the ways that we seek input when we want to get information from the public, one thing we do is we convene advisory committees or subcommittees such as this one where we bring in experts to sit at a table and discuss things, so that we can hear their dialogue.

Another way we do things is to seek a different kind of public hearing that we call a -- It's called a Part 15 hearing where we sit at the table, and the public comes and gives us testimony on what they think about a particular topic. So they are almost the reverse of what we have here today.

Next slide. So here's our first transition. This is an introduction to labeling.

Just to sort of set the stage, FDA regulates drugs and biologic products. Well, what does that mean?

That means that we oversee and ensure that patients are protected and that development is not too wild and crazy from the time that a drug first goes into humans until the time of marketing.

At the time a company wants to market a drug or biologic product, they bring before us an application that contains all of the relevant safety data and efficacy data about that product in support of their marketing application.

So we review data that's provided by pharmaceutical sponsors. Contrary to what lots of people think, we do not conduct primary clinical research. We rely on the data -- make our decisions based on the data that's provided to us.

The system we have really is a very intensive, final vetting process to ensure that data on safety and efficacy of products is indeed what the pharmaceutical sponsor says it is. Next slide.

The final printed label or this thing represents exactly what an individual product is

approved or licensed for. Drugs are approved for marketing. Biologics are licensed. People use the terms -- often use the terms interchangeably, but there is a subtle difference.

This label, the final printed label, really summarizes what we and the company consider the key data about a product for medical professionals. It's important to keep in mind that the commercial sponsor or the company -- in this case, it's Pfizer -- owns this document. It's a legal document, and it has an intricate link to product promotion.

Because of that, we at FDA pay particularly close attention to what's in here regarding the indications for use, because sponsors cannot promote use in advertising for anything that's not in here, and what safety information this contains to ensure that health professionals are adequately apprised of risks. Next slide.

Once a product is marketed, the commercial sponsor has several obligations under law. One of those is to, on a periodic basis that's set by law, report safety data to the FDA and to propose label

changes to reflect new data, particularly safety data.

Sometimes FDA acquires data that we think warrants a label change, and it has happened in the pregnancy area occasionally, but it's really the exception. Frankly, we just don't have the resources to do that on a regular basis. Next slide.

Now important corollaries are that FDA doesn't regulate the practice of medicine. Well, what does that mean? We approve products for the treatment of conditions that are listed in the label under the "indication" section. So treatment of hypertension, for instance.

The pregnancy section is not an indication section. It adds information -- usually, it's safety information -- much like the sections on geriatrics and pediatrics. So products, contrary to what I hear many people ask -- have many people ask me questions about, products are not indicated or not indicated in pregnancy per the labeling, with the exception probably of what we know as Category X where there's thought to be a contraindication.

Let me give you an example, and I just

think this is important for you to sort of understand the whole picture here. I was at an academic meeting a few years ago, and a woman who was giving a talk stood up and was talking about a particular product and a particular use in pregnancy.

She said, and we know that this works in pregnant patients just as well as in other patients, but the FDA won't let us use it. Dr. Montella knows who that was. She was there.

That's not true. It's not up to the FDA whether anyone can use a product in pregnancy or study a product in pregnancy per the label. The pregnancy section of the label is intended to provide safety data or risk information for the practitioner who is faced with the adult patient or adolescent patient who is pregnant. So there is a difference there. Next slide.

So that's Labeling 101. Now I'm going to tell you a little bit about the pregnancy section of the label. This was first added to our requirements to include in labeling by regulation in 1979, and the intent of this section and the rule governing it was

to assist physicians who are faced with making prescribing decisions for pregnant patients.

I actually went back and read the preamble to the regulations to get a good flavor for this. There was never any intent of this regulation to facilitate decision making about what we all inadvertent exposure or retrospective risk considerations, what to advise the patient who has already been exposed without knowledge that she was pregnant.

It was really the former, to assist in active prescribing before exposure has occurred, and we'll get into a little more of that later. It's intent was really to take complex information and put risk and benefit together in a simplified system marked by letters. Next slide.

I know that most of you are familiar with these, but some folks in the audience may not be. So I'm just going to walk through the categories quickly.

Category A: The criteria for Category A in the regulations say that there must be adequate and well controlled studies in pregnant patients that

demonstrate no risk. We all know how many of those there are.

I think at last count we had five or six, and they were, I think, insulin and several thyroid hormone replacements and maybe an iron supplement. I'm not sure. But we all know how likely this is, in the absence of a product specifically to treat a condition associated with pregnancy such as pre-term labor. So we have very few of those.

Category B: The criteria for Category B are that animal studies show no evidence of risk. Animal studies are clean or, if they are positive and show some ill effects of the drug in animal reproductive tox studies, the human data override that or are somehow reassuring. It's not very well defined. About 18 percent of drugs currently in the PDR have Category B assigned. Next.

Category C is -- The requirement for Category C is that human data are lacking, and animal studies are either positive or they don't exist. They weren't done. About two-thirds of drugs are assigned Category C, which in some ways makes sense, because

new products come to the market.

They aren't usually -- There aren't usually any human data. So animal studies are often positive, and I'll say a few more words about that, and we don't have any human data. So there goes Category C.

Interestingly, if you look at the drugs that are in the PDR, about 40 percent that actually have Category C assigned have no animal studies. So there's no human data, no animal data. That should be changing, because we now require animal studies, but in the early years of the application of the regulations, those requirements were not as stringent as we have now. Next slide, John.

Category D: In Category D, the criteria is that human data suggests risk, but the benefit, the clinical benefit to the patient, may outweigh that risk. Interestingly, if you look through all the Category Ds, most of them are assigned Category D based on animal data. We haven't actually followed our own rule.

Category X indicate that animal or human

data are positive, and in general the potential benefit of the product does not outweigh the risk. Most of the drugs in Category X are actually assigned an X on the basis of the combination of that animal data and what's thought to be -- The term that's tossed around, a trivial indication. But most of them are not based on human data. Next slide.

Now our experience in applying these categories over 20 years has been somewhat frustrating. Some people like the category. They find comfort in it. Other people get very frustrated by it.

The reality has been that for us most products do have only animal data when they come to us. If you think about the nature of animal toxicology studies, whether they are reproductive toxicology studies or non-reproductive toxicology studies, the way they're done is they're done so that you will see toxicity. That's the idea here.

So unless you have a product that's incredibly inert, for the most part, you're going to have positive findings. Ergo, Category C is the norm.

On the other hand, we are frustrated ourselves by the fact that we don't -- Although we recognize the value of these animal reproductive toxicology studies, the specific predictive value and translation of a toxicity in animals to organ system by organ system is not necessarily a perfect line, and there are a lot of unknowns that we struggle with.

We've also been frustrated by the fact that we have this complex, very what we see as rigid category system with no concomitant requirements on our labels that sponsors specifically address any updated information in their safety reports on marketed products to us. It's nice if they do, but we don't have any real forthright statement in our safety regulations that say you will do this, we think this is important.

Third, we also -- and this is a subjective assessment. We recognize that for many pharmaceutical companies, having big cross-marks and warnings in a label is perceived as a good thing. That is not uniform, and I think it's changing. But for a long time we have been faced with that, where companies

don't want a Category B, for instance. They like having a Category D on the basis of animal data, because their legal counsel sees it as a liability protection.

We've also found that we have this regulation that's very complex and says here's how we define these different categories, and they are defined in such a way as it's extremely difficult to change once you have a category.

It's extremely difficult to go from a D to a C, and it's especially tough to go from a C to a B or an A. The reason is that you have bad animal data, and you can't make it go away. It's always there.

Finally, as many of you know and have been involved with, we've had a lot of criticism of these categories from external sources over the two decades of their use. Next slide.

I think, as Mac already pointed out in his introductory remarks, our biggest frustration is the same frustration that clinicians in practice feel. The biggest challenge in all this and the reason it's so difficult is because this is an area of medicine

where we desire the greatest certainty.

The stakes are extremely high if you're wrong, but we are frustrated by the fact that we have absolutely the least data in quantity and, for the most part, in quality when it comes to human data. Next slide.

So Part III. With that in mind, the agency established the Pregnancy Labeling Task Force. This task force is actually made up of members from all five FDA centers, not just Drugs and Biologics, and we have -- the Task Force as given three major tasks.

One is to examine the current regulations. The second task was to make recommendations for changes, which is why we're here today, and the third task was to consider the bigger picture of related needs.

I'm going to spend a fair amount of time going through number one, which is listed as A next, on examining the current regulations; because I'd like to get that done and be able to close that for the day. The recommended changes I will touch on. We'll

have a more formal presentation later. But I'll also give you a flavor of some of the other bigger picture items that we're trying to tackle. Next slide.

So to examine the current regulations, we decided we really needed some broad public input. We all knew what we thought, as I told you about our own experience, although we couldn't agree on anything. So we held a public hearing, a Part 15 hearing, in September of 1997, and many of the people at the table were actually at that meeting.

We asked these questions: Is this system of labeling relied upon by practicing providers? Is it useful? How so or how not so? What do you think is good about it, and what's bad about it? And if overall you think that it's not informative, as we suspected many would, or you think it's excessively problematic, what can be done to improve it? Next slide.

This is a representation of just a few of the organizations that participated and came to that Part 15 hearing to provide oral testimony. In addition, we had consumers. We had representatives of

consumer groups, societies. We also had a fair amount of written testimony that supplemented this. Next.

I'm going to summarize all of the feedback that we had. I will tell you, it was a very long eight hours. So I'm sparing you. You're only going to get six slides on this, I think. I'll go through the positive aspects, the criticisms, and then the recommendations. Next.

So although, as I said, I have a few slides, we can sum up the positive comments in one slide. One was that the information is relied upon by practitioners, and the number one positive comment was, well, you know, the idea of having a simplified system is a good idea. It's kind of nice. You can condense this information down to a single category, a letter system. It seems orderly. We like the idea that it seems orderly.

It fits nicely into little tables for pocket handbooks that you can carry in your lab book, and our residents use them that way all the time. Because it's simple, clinicians don't -- when they're in a hurry, don't have to interpret -- try to

interpret complex data, and it is familiar. Everyone knows the system. So that was thought to be a positive. It's just sort of general recognition and acknowledgment that everyone is using the same thing.

So there ends the positive comments. Let's go on to the criticisms. The first criticism is exactly the reverse of what people liked about it, and the criticism which was overwhelming was that this is an overly simplistic system. It's deceptively simple. This isn't as simple as this letter system implies.

Many, many examples were provided. If you think about it, it looks like grades in school. A is better than C. B is better than C, etcetera, etcetera, which is not always the case.

It appears that this is risk graded, that A, B, C is a risk gradation when, in fact, that is not the case. There was a great deal of concern about the fact that this system fosters a passive approach to very complex clinical situations and judgments and is often misapplied and further, that this grouping, these letter categories, often group unlike risks together.

That gets back to the concept I think I introduced before about Category C. A C is not a C is not a C. It can be based on very different information. Next.

There was concern about the heavy focus in the system and at least what finally makes it to the label on teratogenesis, often to the exclusion of other important fetal endpoints. In particular, often the relevance of the animal dosing in the animal reproductive tox studies doesn't seem to be taken into account or it's not obvious that it has been.

Further, the descriptions rarely address maternal toxicity issue, and actually there are two different maternal toxicity issues in the animal studies; and labels rarely address the role of maternal toxicity and how that impacts on the findings in the animal offspring. But also we rarely address maternal toxicity to the mother, to the pregnant woman. Next.

Risk/benefit considerations, although this is supposed to be a risk/benefit balanced system, are often incomplete, and specific areas that they often

don't address include the individual -- taking into account the individual risks to the mother and fetus of no treatment of a particular condition. Examples of that might be hyperthyroidism or diabetes.

They also often don't consider any risks within the context of population risks of adverse outcomes, either all comers or any individual one of concern.

Further, they don't address the risks to the fetus posed by the maternal condition itself independent of treatment. An example of that I could probably use is maternal epilepsy. Next slide.

As expected, because I told you about the original intent of this system, it really doesn't facilitate assisting the physician faced with retrospective considerations of risk. I have a quote up here. I think it was John Desesso who said at the meeting, "Deciding what to prescribe is not the same as deciding what to advise patients once exposure has occurred."

Anybody who has ever been in a practice situation like this knows that very well, and it's

particularly relevant that recent estimates of family planning in the United States indicate that at least 60 percent of pregnancies are unplanned. So folks may be faced with this quite often.

It's made even more frustrating by a system that doesn't discriminate in assigning a risk between suggested effects from preliminary animal studies compared to known effects in humans. You can have the same thing in Category C, for example. Next slide.

There were concerns that the data underlying the categories aren't well described and are really not informative, even to readers who know a lot and are interested in knowing more.

Further, the human data is rarely presented even when it's well known and in the medical literature. That was really raised as much as a credibility issue as anything else.

Finally, the labels rarely indicate whether there are degrees of risk posed by timing or extent of exposure to a given product. Next.

After all this, I would say we just

thought -- We just kind of sat there and said, oh, my god, we knew it was bad, but walking through all these was pretty demoralizing. Really, we recognize that the current system is generally uninformative, and it probably needs to be replaced and not revised.

It was so clear that it was that far gone. What was very striking about the testimony was how risk communication and the concepts underlying it, particularly in this area, have increased in sophistication over the 20 years since the regulations that we have in place were promulgated, and we really need to do better.

Now we did get some -- We were able to tease out of all those criticisms some specific recommendations. We got very little in the way of how to do this better, which is understandable. So we had to tease some out, but there were some clear messages, and those are on the next slide.

First was that the current category system really should be replaced with narrative descriptions of risk. Actually, that was a comment that was made -- has been made repeatedly.

Second, that we really need to pay attention to varied readership needs. People hear things differently, and we talk about risk qualitatively or quantitatively. The access -- The intellectual access to risk information between a physician and a nurse practitioner and a pharmacist and a patient may be very different.

Third, that we need to be careful to distinguish any clinical advise in labeling from risk information. Now what does that mean? Well, it was quite clear that this is a very important distinction, and it's an important distinction particularly because giving advise in a label is very different than a curbside chat between a generalist and a specialist or a physician and a pharmacist or even several of us in a room at the FDA.

This carries a different weight. Some of it is psychological weight. Some of it may be perceived as a liability weight. So we need to be careful to distinguish that and be careful.

We need to provide underlying data that's more comprehensive and clear than we've done in the

past. Finally, we really need to do a better job with language, and there were a number of comments that I didn't go into in detail here about some of the emotional charge that much of the language in this section of the label have come to carry over years.

I don't think it was ever intended to be that way, and it probably wasn't that way 20 years ago. So next slide.

So our second task of the task force was to make recommendations for changes in labeling. We began this by taking all of that feedback that I just summarized for you and tried to put together a draft model, a very simple model for labeling that tries to anticipate problems and incorporates some of the concerns that have been raised.

Dr. Behrman is going to present the model formally to you -- you have it in your packet -- a little later this morning, just before you embark on the discussion. But that's where it came from, and it wasn't easy to put this model together. I will tell you, it was agony.

Joe DeGeorge is over there laughing. It

was very difficult. We understood why there weren't many specific recommendations by people at that Part 15 hearing. This is really hard. Next slide.

So what I'm going to move to now is the third task of the Pregnancy Labeling Task Force, which is think. Think more broadly about the needs of pregnancy labeling. What are the other pieces of this complex puzzle that need to be put in place to do this better? Next slide.

There are many pieces, and they really come down to FDA expertise, using outside expertise, dialogue and communication, and data, data collection, generation and quality and what the science is underlying all of that. Next.

First, FDA expertise, and I'm going to start with the first piece, which is clinical expertise. You know, if you look at the doctors at FDA, we're like most doctors. We have not -- We, with few exceptions of a few of us, there's -- You know, most of us have not had very much experience taking care of pregnant patients.

For instance, in my divisions where we

oversee the regulation of drugs to treat infections, most of the docs have infectious disease training. So they understand what it's like to say things in a label about the use of an anti-infective product, because they do that.

Most of them have not treated very many pregnant women, and they like it that way. That's just reality. So it's difficult for them to put themselves in the clinical context of the end user of this information in the labeling.

It's a challenge. It's not something they think about every day, and we need to do a better job of educating those reviewers and trying to facilitate that and give them confidence in what to even begin to think about when they're faced particularly with human data.

What we get, as you might imagine, is a product is on the market, and we get a couple of reports through our MedWatch system or from the company of birth defects in a woman who took Product X. Well, what do you do with that?

So we have embarked on an intensive system

of trying to give a comprehensive view to the medical officers about how to think about those problems. We've started with a very rudimentary reviewer's guidance document -- here are some general things to think about -- and implemented a system of training that has been extremely enthusiastically received by our reviewers.

We've used outside experts as well as folks inside to do this, because we sure don't have -- The few of us who are there doing this don't have all the knowledge. Tony Scialli has been particularly helpful to us in this. He couldn't be here today, but this is near and dear to his heart, as many of you who know him know.

We're doing the same thing in the area of preclinical expertise, but in some ways more so. We are looking -- We are trying to document an integrated approach to how we review reproductive toxicology data.

This is not my area of expertise. That's for sure. So as not to embarrass myself or the agency, I'm going to have Dave Morse, who is an expert

in this, give you a summary of some of those activities after my talk. I think you'll find it very interesting. Next.

What about improving data? I mean, after all, that's what we really want in the end. In the area of collection, we are in the process of drafting a new safety reporting regulation that's very comprehensive and that meets criteria set under the International Conference on Harmonization, which is the United States, Japan, the European Union, and Canada.

What's unique about this to our discussions today is that this new safety reporting regulation identifies pregnant women as a special population of interest. It actually will say to companies, we think that when you report to us periodically on your marketed products, we want you to tell us something about what's happening with your product and these special populations, and the first one mentioned is pregnant women.

We've never had a rule like this before. It's a small step, but it sends a big message that we

think this is important, and it's one of the ways that we have learned over the years we start to drive data generation.

Another way we've done this is we've put together an industry guidance document -- remember I told you about the guidance documents; you have a copy in your packet -- on establishing pregnancy registries.

We did this, because companies come to us and say, you know, we'd like to collect data; we know this product is being used by pregnant women. We'd like to collect data, but my God, we don't know where to begin; can somebody help us?

There's nothing out there in the medical literature on this. So we send them to Elizabeth Andrews or to Janet Cragen at the CDC and say we know these are people who know something about this. But they get kind of tired of us having everybody sent to them. We thought we should put something in writing.

We also found that a number of companies would say, oh, we have a pregnancy registry, and we would say great. And they would come in with their

registry data, and really what it was, was it was that they had a separate drawer in their file cabinet where they collected adverse event reports on pregnant patients, which those of you who are in this business know is not quite the same.

So we think that this draft guidance document at least begins to set a standard for data quality. Next.

Other possibilities that we're looking at to try and glue this together are finding ways to simplify for pregnancy registry development, and better use of the FDA Website to provide more comprehensive information about pregnancy risks. After all, there's only so much space in a label.

To do some of these things, we recognize that over time we need to be working on this intensively through partnerships within government and outside of it, and we've already begun to do that. Next slide.

So finally, I want to set forth our objectives for today, and there are really only two, as I think I said in my introductory letter.

First is to seek your input and general guidance regarding our progress to date with development of a new label model, as will be outlined in the concept paper later this morning.

It's not to add to our database from the Part 15 hearing on what's wrong with what we currently have, and that's why I spent so much time on it. I kind of wanted to get it out of our system.

We need to move forward, and we need your help in going in the right direction. So what we'd like to hear from you are suggestions, comments, practical considerations on the format and content of what we've proposed and what it will be like to apply that.

Second is we would like to seek your input on what I think is the more difficult issue of how best to use language to communicate risk information and management advice.

You know, if this seems like it's tough to get your arms around, it is, and it is a critical aspect of labeling that really has been given very little directed attention in any area of the label.

We often -- At FDA, we know who the people are in our organization who do labels really well, and one of the reasons they do them well, if we think about it, is because they understand this. They understand how to use language, which, you know, most of the rest of us don't really think about in an active way.

So we'd like you to try and think about that. Think freely. Okay? Brainstorm. That's okay. One of the reasons this is particularly critical is because we have a broad spectrum of label users who have different needs and different access intellectually to information that comes often from the way it's presented.

So finally, some helpful hints: If this seems difficult, it's because it is. We seek your general guidance. Consensus helps, but you don't have to have consensus. I think it's unrealistic to think that you will all agree on any particular item.

You don't have to vote on things, if you don't want to. That's up to you all. But if you don't reach consensus, it's very helpful for us to

understand why that's the case, why there are disparities, and try to think about ways that we need to go about addressing that.

I finally just want to reassure you, because I've had a couple of questions on this, that FDA's responsibility is to write the new regulation. You don't have to do that. Okay?

We actually have people who do this, you know, that sit and think about how to write these things with some help from us. So even the people at the table here, we don't do this, and you sure don't have to do it either.

So with that, I'm going to close. Dr. Greene, it's up to you if you want to have people ask any questions now or hold them for later. It's your call.

CHAIRMAN GREENE: It seems that we're doing well on time, I think. Let's see. Dr. Morse is next. Actually, why don't we hear from Dr. Morse, and then we'll see how we're doing on time. Please.

DR. MORSE: Good morning. My name is David Morse. I'm a toxicologist in the Division of

Antiviral Drug Products, which is part of the Office of Review and Management in ODE IV, which Dr. Kweder heads at this time.

I'm also the current Chairman of the Reproductive Toxicology Committee of the Center for Drugs, and this is a relatively new position for me. So I'm not going to talk about the past. I'm going to only talk about moving into the future.

As Dr. Kweder has already alluded, the FDA's Pregnancy Labeling Task Force oversees a multi-factorial effort to review the content and the quality of information presented in the pregnancy section of prescription drug labeling.

The Pregnancy Labeling Task Force has identified the need to assist both the preclinical and clinical specialist alike with the interpretation of findings from animal and human studies of reproduction effects resulting from drug exposure.

The CDER Reproductive Toxicology Committee has been charged by the Pregnancy Labeling Task Force with the responsibility of developing an integrated approach to the nonclinical reproductive toxicity

assessment. If I could have the next slide.

In a schematic form, this is the process that we're going through at this particular time, the Pregnancy Labeling Task Force here, Multi-Center, this advisory committee serving a role with the Pregnancy Labeling Task Force, and broadly speaking, there is a separation between the clinical study evaluation which Dr. Kweder just spoke to and the nonclinical studies evaluation area, both of which ultimately feed into the label format and the content.

Within the nonclinical studies evaluation area, there is the reproductive toxicity committee, the Reproductive Toxicity Education Subcommittee, and the Pregnancy Integration Working Group, which I'm going to go through some information about each one of those and their current function.

There are a number of things that I'd like to present dealing with changes in structure, function and the content of changes which are being made within the nonclinical studies evaluation area in response to the charge from the Pregnancy Labeling Task Force. If I could have the next slide.

As I said, within the nonclinical studies area there is the Reproductive Toxicity Committee. This is chartered within the Center for Drug Evaluation and Research. There is the Reproductive Toxicity Education Subcommittee which answers to the Reproductive Toxicity Committee, and the Pregnancy Integration Working Group which also is a subcommittee of the Reproductive Toxicity Committee. If I could have the next slide.

So the Reproductive Toxicity Committee has several functions and initiatives currently that it's working on. It serves as a consultation service for review divisions regarding the design, the content, the analysis and the interpretation of reproductive and developmental toxicity studies that have been submitted to the agency by pharmaceutical sponsors.

It also serves as a forum for the discussion and the resolution of disparate interpretations of study data. It attempts to promote consistency in study data interpretation and the application of appropriate rules and regulations as they currently stand, and as they may stand in the

future, and it also right now is attempting to develop a reviewer handbook.

This is basically a background package for use by reviewers within the agency on reproductive toxicity testing, including considerations of design and reference information for commonly used animal models, data analysis procedures and practices, as they currently are being conducted. If I could have the next slide.

The Reproductive Toxicity Education Subcommittee has several functions, including the defining a core curriculum for education in reproductive toxicity, developing specific course curricula and promoting the dissemination of information, and this is done through seminars, presentations at national and international meetings, the presentation of staff college courses -- these are basically an internal education process for reviewers within the agency -- and publication of current -- or guidelines and papers dealing with current practices and perceptions on reproductive toxicology. If I could have the next slide.

Now probably of greatest interest to this particular committee is the work of the Pregnancy Integration Working Group. This particular group -- The specific objectives were to develop a new and more effective evaluative method to judge the adequacy of nonclinical reproductive toxicity study data, and to organize the study findings for more effective communication to others. So for instance, what would go into product labels. If I could have the next slide.

Now the Pregnancy Integration Group had several goals for the outcome of this new process: To effectively integrate nonclinical study data from developmental and reproductive toxicity studies with all other available pharmacologic and toxicologic data.

As Dr. Kweder already indicated to you, the current labeling practice predominates in the area of teratogenicity and does not take into account in the regulation information dealing with many other endpoints of reproduction.

Also the goals for this integration

process were to enhance the scientific consistency with which developmental and reproductive toxicity studies are evaluated. If I could have the next slide.

So the approach that was taken by this particular group was to enumerate and codify the thought processes of a number of experts in reproductive toxicity testing and of the regulatory sciences in assessing drug induced reproductive risks. This was not a simple process, to say the least. If I could have the next slide.

To define the process, we developed a tool which reflects the conventional thought processes of these experts drawn from multiple centers within the FDA as they apply to the interpretation of findings from studies of reproductive and developmental toxicity.

Now the next slide that I'm going to show you is a rather complex one, but it represents the integration tool for positive reproductive endpoints that have been detected in any reproductive developmental or general toxicology study as it would

be submitted to the agency.

I'm going to break this down into several subunits in my next few slides, but let me just say at this point that this figure starts with a positive signal. There are seven reproductive endpoints which I will go into in just a moment, each one of which can demonstrate a positive signal and, therefore, would go through this evaluation process.

If they demonstrate no signal, they go through a separate evaluation process which I'm not going to bother to go through today, just based on the amount of time available.

The process begins with the animal data. It looks at characteristics of the signal that is seen in the animal studies. If you wanted to break this out, this would be the responses in the offspring or the F-1 generation. This would be more related to signals as seen in the F-0 generation or the Moms.

Here we have pharmacodynamics of the response, the general toxicology and drug disposition characteristics, both in the animal species and in human.

Here in the middle of the integration process we're dealing with basically a mutual evaluation of the characteristics of the drug as it is in the animals and also in humans, that being based on prior clinical trials data.

The exposure data, the relative exposure between the animals and humans, is taken into account, and then ultimately class alerts being based on prior experience with a similar structural entity or a compound with related pharmacologic effects, as it has been demonstrated in humans.

This ultimately results in assignment of risk, high, medium, low or no risk. If I could have the next slide.

The integration tool: There are several general considerations. It is a stepwise or hierarchical process. It begins with the animal findings and progresses to findings in humans. It is a weight of evidence approach based on the nature and the quality of the applicable toxicity data that is available at the time that the product is labeled or that becomes available subsequent to that time.

It is a hazard or risk identification. The previous system included both risk and benefit in one summary categorization, A through X. This process, as I've just described it to you, is separating out hazard identification or risk identification. Clinical management will be a separate step in the process and will be separately described and enumerated. If I could have the next slide.

The integration tool also -- There are several additional considerations. It's a series of questions asked of each of the seven reproductive endpoints. Adequate quality, human data takes precedence over nonclinical study data, and there are different questions for positive and negative endpoints, as I stated before.

Negative endpoints are run through a different process that simply asks questions about the adequacy of the study conduct and the manner in which the data were interpreted for the findings there. If I could have the next slide.

The integration tool begins the process

with positive signals for any one of seven defined reproductive endpoints. We have reproductive toxicity endpoints which include fertility and fecundity, parturition and lactation.

'So F-0 generation developmental toxicity, F-1 generation developmental mortality, dysmorphogenesis, alterations to growth and functional toxicity. The prior labeling practices have generally focused on dysmorphogenesis or teratogenicity. If I could have the next slide.

The six factors: These were the columns that were on that diagrammatic that I just showed a few moments ago. It's broken out. The level of concern for a positive signal is affected by the evaluation of the signal strength within the F-1 generation, the G-0 generation, the pharmacodynamics. This is concordance, basically, between the drug disposition and metabolism in the animal species and in the human.

The human and test species, concordance of general toxicity profiles and drug metabolism, relative drug exposure -- This is something which is

very important. Obviously, if you see a toxic endpoint in the animal studies at a thousandfold, what you're going to see in the clinic, there's clearly going to be a significant modification of your level of concern than if you see toxicity in the animal studies at a fraction of the human exposure.

Then, of course, prior experience in humans with structurally related compounds or compounds with a similar pharmacologic effect. If I could have the next slide.

So why is it that we need this process? Well, other than the fact the Pregnancy Labeling Task Force has said that we're going to change and that we need to change and that the Part 15 hearings clearly demonstrated that there was a very vocal constituency that said that we needed to change and tat we should change, there are other reasons to change the process.

First is to assist in the interpretation and the integration of reproductive toxicity study findings within the agency and across the various components of the agency; to promote consistency in the interpretation of reproductive toxicity study

findings both within and across divisions within the agency and in dealing with pharmaceutical sponsors; and to provide a common framework for the review, the interpretation and the discussion of findings between all interested parties, so that everyone at least has some fundamentally similar working basis for the discussion of how they interpret the significance of reproductive findings.

With that, given that I have relatively limited time, I'm going to end my talk except to go on to the next slide and say that, as the ICH guidelines for reproductive study design say, this is a starting point. It's not an endpoint.

It's just a beginning point to initiate a discussion on how to interpret study findings and where to go with it from there. It's not the end-all and be-all and has never been intended to be so. If I could have the last slide.

Probably the group of individuals who has put the most effort in has been those involved in the Pregnancy Integration Working Group, and I would like to give them special recognition at this particular

time.

Current members of this group include Paul Andrews, Joe DeGeorge, our Associate Director for Pharmacology and Toxicology, Jim Farrelly, Ed Fisher, Abby Jacobs, myself and Mark Vogel, and several current members who have now gone off to industry, and Mary Ellen McNerney and Hillary Sheevers.

So with that, I think I will end my presentation and ask if there are any questions.

DR. WISNER: I have two questions.

CHAIRMAN GREENE: We're making a transcript. So please identify yourself.

DR. WISNER: Oh, it's Dr. Kathy Wisner.

I have two questions. The first is: Is there a specified sequence of animal models in which new drugs are tested?

The second is: Can you give some examples of the kinds of functional or developmental outcomes that you assess in the F-1 generations?

DR. MORSE: Well, in terms of specific animal models, there are a number of animal models that are frequently used or typically used which are

based on historical databases, the availability of comparative historical information, general conceptualization amongst toxicologists, the industry that these models are acceptable to the regulatory agencies, whether it be FDA but also EPA and other regulatory agencies.

Of course, we are dealing in an international forum. So we have to take into account the fact that sponsors will be submitting the same results not only to the FDA but also to the EU and to the Japanese regulatory agencies. So they are interested, obviously, in using animal models that are going to be acceptable to all of those regulatory agencies.

There are some instances, however, in which the generally used animal models are known not to necessarily be applicable to a particular product. For instance, the interferons might be a good example of that particular area, because most of the generally used animal models, rodents, do not have the necessary receptors to respond to the interferons in an effective manner.

So in order to effective test those, you would need to move to a primate model with appropriate receptor populations. Certainly, that would be taken into account in the design and the conduct of any study.

As to your second question, if you could reiterate that, please.

DR. WISNER: I was interested in the kinds of developmental or functional outcomes you look at in animal models, and probably more specifically, how relevant those might be to humans.

DR. MORSE: Well, generally speaking, the functional endpoints focus in on development of the nervous system. Development in most other areas, in most functional capacities of organisms -- they certainly can be measured, but they typically are not.

The primary focus has been historically on development of cognitive function and the nervous system in general.

DR. O'LOUGHLIN: Victoria O'Loughlin.

The question I had was: In your integration tool, how are you setting your tolerances

or thresholds for each of your factor points going through to determine your high, medium and low, and do you have a continuous improvement process to look at those tolerances over and over again to make sure that high, medium and low really mean something?

DR. MORSE: We could maybe go back to that slide, John. As I said, right at the moment this is a qualitative process. It's based on a weight of evidence approach.

There is really no way of specifically assigning at this particular point, at least in the opinion of this committee, and there is going to be a meeting later on this month on June 24th, an FDA/industry workshop specifically discussing this tool, and I'm assuming that we probably will get feedback on exactly that particular aspect of this particular tool.

Basically, in reviewing a product these six categories are treated equally. They're given equal weight except for here with class alerts and with human data. Human data can override any and everything that you find previously and that you

estimate from the animal studies.

Class alerts, being also based on prior human experience, is given a significantly greater degree of emphasis, which is why it's presented at the righthand side of the figure. It can overrule, basically, pretty much everything else.

For each one of these factors, the review process calls for a general weight of evidence, a conception of either a general increase, no change or a decrease in the overall level of concern. At the end here, you summate the weights given to each one of those categories, and it is a simple sum that results in the estimation of significant, low, medium or no known risk.

CHAIRMAN GREENE: Thank you very much, Dr. Morse. I think I'd like to move on to try to keep the program close to on time.

I'd like to ask Dr. Holmboe, please.

DR. HOLMBOE: Good morning. Thanks, John, for the slides. My name is Eric Holmboe. I'm currently a general internist at the National Medical Center, but I became interested in risk communication

during my fellowship with the Robert Wood Johnson Foundation, and Sandra was nice enough to ask me to come today to talk to you a little bit about the perils and pitfalls in talking about medical risk, which is certainly pertinent to this committee.

I think some of the things you heard earlier from Sandra will resonate in some of the difficulties I'm about to talk about and some of the challenges involved when we discuss medical risk, particularly with drug labeling in pregnancy; because as Sandra pointed out, oftentimes we don't even have the data with which to discuss risk about, and it's tough enough when you do have the data, as I'm going to try to highlight this morning.

Can I have the next slide, please. Well, very simply, kind of a Risk 101, as Sandra talked about earlier, what is risk? Well, this is how Webster's dictionary defines it: 1. a dangerous element or factor; 2. possibility of loss or injury; and 3. the degree of probability of such loss.

Next slide, please. So what is risk? Well, the concept of risk essentially embodies at

least two distinct notions. The first, as we saw on the definition, an unwanted outcome that's combined with some uncertainty about its occurrence or probability. Next slide, please.

So as you can see, understanding risk is really a complex task that must combine the subjective information with subjective interpretation, and it's really this other point, subjective interpretation, which you can think of as kind of the third aspect of risk. Risk has to be interpreted and perceived by the individual using that information. As we'll see, this can sometimes be very difficult.

Next slide, please. What I'd like to do now is just provide you with kind of a basic framework to think about some of the elements of risk. I've listed just five. There are others, but the five that I want to talk about a little bit this morning are identification, permanence, timing, probability, and value where you might think of that as subjective badness. Next slide, please.

Let's talk about the first element, or identification. Identification of the unwanted

outcome or risk is really the first task of the physician. What are the challenges?

Well, are all of the risks known? I think you heard that when it comes to drugs in pregnancy, that is often not necessarily the case.

Number two, is it a risk, a benefit or both? As Sandra alluded to earlier with regards to seizures in pregnancy, there may be a risk associated with the drug to the fetus, but the seizures themselves may be a problem. So controlling the seizures with a drug may actually be more of a benefit than a risk, and sometimes it's very hard to tell where that balance lies between risk and benefit.

Finally, is discussion of risk even part of the medical encounter? In other words, is the risk identified to the patient? Next slide, please.

With regard to this last point, I just want to point out a couple of studies that have been done. The first was done by Kalet in 1994 where he audio taped 160 patient visits among 19 community based practitioners, mostly internists and family practitioners.

What he found in those video tapes was that risk was not discussed routinely and, when it was discussed, risk was rarely given in quantitative terms. Next slide, please.

In some work I did on my fellowship with angioplasty patients, we were interested to find out what they knew just prior to their procedure. So we interviewed patients who were scheduled for angio -- I'm sorry, elective angioplasty the day before their procedure.

What we found was the following, that only 46 percent of patients could even recall a single possible risk of the procedure they were about to undergo. Twenty-five percent offered spontaneously that they did not have any discussion of risk with their doctor, and that most patients actually wanted to have a major role in determining the acceptability of the risk and benefit of this particular procedure.

Next slide, please. The second element we could label is permanence. Is the risk only temporary or is it permanent? What are the challenges?

Well, this is not always clear-cut. For

example, low birth weight -- is it really just a temporary state or is it a marker for more permanent change or risk over time?

With regards to men who have to choose therapy for localized prostate cancer, incontinence and impotence may be temporary or it may be permanent after something like a radical prostatectomy. Sometimes you can't tell until time passes. Next slide, please.

The third element is timing. When will the unwanted outcome occur? Again, the challenge, now versus later? In my angioplasty study, infarction and bleeding are risks that are associated with the procedure in the immediate peri period. However, re-stenosis is a risk that occurs later for a substantial portion of patients.

Then again in pregnancy, you have the immediate versus delayed effects of drugs taken during pregnancy. Are there long term effects that we're not able to measure at the time of delivery that may not show up until sometime later, again a major challenge, I know, for all of you. Next slide, please.

Probability: How likely is the unwanted outcome, and what are the challenges? Well, first probability is often known in varying degrees of certainty, and sometimes that varying degrees of certainty can be zero. We may not know at all.

The other problem with probability is that the application of population derived numbers to the individual patient can be very problematic. Even in the best randomized controlled trials, what do your results basically consist of? It's an average of a large group of patients that represents a range of other patients.

Where does your patient fall in that continuum? Does the patient represent the average patient as a result of even the best randomized controlled trials? It's sometimes very hard to know.

Would that patient have even been randomized to that trial, the whole issue of generalizability. So even if you have good data, and even if you know something about the unwanted outcome, how does it affect the individual patient?

Again, Sandra alluded to this earlier this

morning, that if you're a physician in the office with a patient -- I've been faced with this, as we all have -- how do you make that information something that's meaningful to the patient at their individual level, because for them the risk is either zero or 100 percent. There's no such thing as a four percent myocardial infarction after angioplasty. For each individual patient, it's pretty much an all or nothing phenomenon. Next slide, please.

Then finally, value. How much does the unwanted outcome matter to the patient? The challenge is that patients will differ on how they rate adverse outcomes. It won't be the same for each patient.

An example that may relate to what you're discussing today is tooth discoloration after tetracycline therapy. For some people that would be catastrophic. For others, that if the drug was really needed, maybe that's not such a big deal to them.

Then again, for prostate cancer in some work I've done, that impotence after treatment for localized prostate cancer varies greatly among the men that I've talked to in another study that we did. For

some, they were far more concerned about getting rid of the cancer, and they could care less about the impotence, where for others it directly impacts on what therapy they chose. Next slide, please.

So given this backdrop, and it's given you kind of some five basic elements of risk when we think about it, how do you discuss risk?

I think of it in at least two major components. The first is which risk should be discussed or labeled or written, and how should that risk be communicated? This is something that, obviously, is of major importance to the committee. How do you communicate risk effectively? Next slide, please.

Let's cover first which risk. There's several things, I think, you need to consider. One is this issue of global versus patient centered. By global, I mean when you discuss risk for label risk, do you talk just about the risk for the patient or do you have to think about societal risk?

What's the risk, for example -- You know, we talk a lot about antibiotics. Is that something I

should talk to my patients each time I prescribe it for a URI, for example, versus just simply centering on what those risks mean to just the patient?

Then you have to decide what standard you're going to use. There's basically two major ones that have evolved over the century, particularly in the work that's been done with informed consent.

The one that was throughout this country through most of the early part of the century was known as a professional standard. In other words, information that would be generally discussed or discussed by community of medical peers.

This standard is not commonly used as much in our country, but it still is throughout the world. In fact, the professional standard is alive and well in Britain.

Then the one that we've kind of evolved to, through the courts and through informed consent, is what's known as the reasonable person standard. In other words, information that a reasonable person would want to be told about the procedure, its benefits and its risk. Next slide, please.

Well, how to communicate risk, and what are some of the challenges in communicating risk? I'm going to talk about four. One is something called the framing effect, the whole issue of qualitative versus quantitative expressions.

If you decide to use a quantitative expression, which one should you use? Then what are some of the common errors in risk interpretation that both physicians and patients make? Next slide, please.

Well, the framing effect is this: How risk and benefit is presented can actually influence patient decision making. It's kind of the half -- the glass being half-full or half-empty analogy.

McNeil in The New England Journal in 1982 did an interesting study where he found that, if he framed certain outcomes for surgery, patients changed their decision making. For examples, patients were more likely to do surgery over radiation for lung cancer when the surgery outcomes are framed as survival benefit versus the risk of death. Next slide, please.

So the next question is how should outcomes be presented? Well, this is a real problem. Qualitative expressions are perhaps more accessible to patients, but they have no specific anchoring at any quantitative level of frequency. So it makes them difficult to use. Next slide, please.

Sorry, this is a busy slide, but I'd like to kind of lead you through it, because I think it's kind of interesting. This is some work of Nakao and Axelrod published in The American Journal of Medicine in 1983.

What they did is they took a group of physicians and patients and asked them to assign a quantitative frequency in percent for each of a number of qualitative expressions, and I've reproduced four of them for you here.

The expressions were: rare, sometimes, frequent, and invariably. Basically, what you can see -- The doctors here -- I'm sorry -- are listed in black, and the patients are in red.

You see that the mean and medians for the percentages that they listed for quantitatively were

pretty much the same for both patients and physicians down through each column here, but the real problem comes when you look at the range. This range actually represents the tenth through 90th percentiles.

You see that it really varies quite a bit. For rare, you know, a pretty short interval, zero to ten percent, but still not necessarily real tight. But look at for "sometimes" and "frequent."

The range among physicians for a quantitative percentage sometimes ranged anywhere from ten to 35 percent. Patients listed anywhere from five to 40 percent. For "frequent" the range for physicians was 50-85 percent, and for patients 40-85 percent. So really a broad range of possibilities for each of these expressions. And for "invariably" patients had a range of 40-100 percent for what that qualitative expression meant quantitatively.

Next slide, please. So given that qualitative expressions may be fraught with difficulty in what they actually mean in a quantitative format, which quantitative expression then should you use?

Well, there are a number of different

choices. One is that, if you're just simply trying to look at outcomes, you may use a percentage or you may express it as a proportion.

If you're trying to compare the outcome between two different therapies or events, there are a number of different statistics you can use. One is a relative risk reduction. The other is absolute risk reduction, and one that's getting a lot of popularity, particularly among epidemiologists, is this statistic known as the number needed to treat.

Next slide, please. Let's find out what happens when you use some of these quantitative expressions, and does it affect the decision making? Well, Malenka gave several scenarios to patients and expressed the results in either relative risk terms or absolute risk terms.

What he found is that patients tended to choose the medication with the outcomes expressed in relative risk terms, even when both medications were equally efficacious. He also found that only 28 percent of patients were able to convert a relative risk to an absolute risk correctly when given

sufficient information.

So how you actually present the results can affect decision making. Next slide, please.

Well, Masur then asked patients how do you want your information presented. I think this slide is very telling, because it really, I think, highlights some of the challenges you have in trying to label information; because what it shows is that, again, patients vary in how they want information presented.

Thirty-two percent of the patients wanted the information given in numerical terms, but fully 35 percent wanted it in words only, or in other words qualitative expressions. Twenty-two percent really didn't care. They would take it in either number or words, and eight percent wanted it in both formats.

Next slide, please. Well, how do physicians do with quantitative expressions, and does the way results are expressed also affect physician decision making? Well, Forrow posed a study in 1992 looking at how physicians would approach the treatment of high cholesterol, depending on how that information

was presented. Again, it was presented either in relative risk terms or absolute risk terms.

What they found is that almost half of the physicians were more likely to treat hypercholesterolemia when the outcomes were expressed as relative reduction versus absolute reduction of risk. So again, even physicians are prone to this bias. Next slide, please.

Finally, I just want to introduce this other term, because I think you'll be seeing a lot of it, the number needed to treat, or sometimes you can convert it to what's known as the number needed to harm.

Basically, what the NNT is, is it's one over the absolute risk reduction, and it tells you how many patients would have to be treated over a given period of time to prevent one adverse outcome or the number needed to treat.

For example, in the Medical Research Council for treatment of mild hypertension, you would have to treat somewhere between 100 to 140 patients over a seven-year period to prevent one stroke, and

that's how that number works.

Dave Sackett, who is one of the kind of grandfathers, along with Alvin Feinstein, of clinical epidemiologies, is a real strong proponent of the number needed to treat, but as point down here, we really don't know what the effect on patients physician decision making is by the use of this statistic.

We're actually doing some work at Bethesda now on patients using the number needed to treat, and I can tell you that in pilot patients don't understand it. They hate it. It just doesn't make any sense to them. I'm not sure it makes much more sense to me either at times.

Next slide, please. Finally, I'd like just to go through some of the common errors that are often made in risk interpretation that clearly relate to some of the things you're talking today. The four I'm going to cover are anchoring bias, availability bias, compression, and miscalibration. Next slide, please.

What is anchoring bias? Well, anchoring

bias is when the estimation of risk is based on the risk of other related events or procedures that are already familiar to the patient. So in other words, they are using that as a kind of anchor that something has happened to them that they know about or has happened to a friend/relative to make a decision about something else that's going to be done that may be related or not related.

Availability bias is where the patient overestimates the risk that received substantial notoriety. It's a shame that Dr. Koren is not here today, but in your big folder there, green folder, there's several articles where he presented information to patients and asked them how likely they would be to terminate pregnancy based on the information given to them for teratogenic potential.

What you find is that a large proportion of women before counseling would actually terminate pregnancy even though the risk may be very small, because they tend to overestimate. Something with regard to the, you know, adverse outcomes of pregnancy is something that often ends up in the news.

Another example of this is breast cancer, particularly for women in their forties, which has received a lot of attention. If you ask women what they think their risk is of breast cancer in their forties, they overestimate it by a factor of almost anywhere from five to tenfold. Again, that's because it was very much part of the media. It's very available to them.

I think that what Dr. Koren has labeled as availability bias would be something known as misinformation, because again of the notoriety, media attention and stuff that it often receives. Next slide, please.

Compression is basically the overestimation of small risk and the underestimation of large risk. This is something that we're all prone to do.

Then finally, miscalibration basically is the overconfidence about the extent and accuracy of one's knowledge. I can't imagine it ever happened to a group of physicians. Next slide, please.

Let's just focus a little bit and talk

about the perception of risk. You know, recall that earlier slide where you had to combine the objective data with the subjective interpretation. I want to just go over a little bit of work done by a gentleman by the name of Paul Slovic who published this article in Science in 1987.

If you're really interested in this area, I recommend you read this article. It's a very nice, short piece, and I think really highlights some things that are very pertinent to this committee.

What he did is that he took various groups of individuals and tried to find out what were really the two main factors that were driving patients' perception of risk. He came up with two factors using factor analysis technique.

The first was known as dread risks. These are risks that are perceived to have a lack of control, catastrophic potential, fatal consequences and inequitable distribution. One example of that would be nuclear weapons and nuclear power plants. Okay? They will be seeing some dread, high catastrophic potential.

Drugs in pregnancy also carry this potential dread because of the catastrophic potential that may happen if you have a bad outcome.

The other factor he called unknown risks. These were things that were unobservable, unknown, new, delayed in manifestation of harm. It also applies to drugs in pregnancy, particularly with new drugs that come out. We really don't know.

The other things that Slovic talked about were things like pesticides and fertilizers. You may remember the big DDT scare, things like alar and apples. All those things were kind of new. We really didn't know what the long term effects of those agents were. Next slide, please.

Now I just want to kind of highlight for you what he did to kind of look at this. He basically took 30 activities or technologies and asked three different groups of individuals to rate the riskiness and ranked them from one to 30 with one representing the highest risk.

This is what he found, that in the League of Women's Voters and among college students, nuclear

power is listed as the number one riskiest activity or technology out of 30. Okay? But experts who worked in the area of technologies ranked it 20th out of 30.

As you can see, these two groups were ranking this high on the basis of both dread and unknown or uncertainty, both types of risk. This scored really high on those two particular axes.

Whereas experts tend to look at what is the annual mortality possibilities from each of these activities or technologies. So the experts tend to look at kind of annual mortality and a lot less of these issues of dread, unknown or uncertainty type risks.

You can see that for surgery, which I would certainly argue should be up in the top ten, you can see experts ranked it pretty high, number 5, but again this group tended to rank it a little bit lower.

Spray cans: Experts ranked it 26, but you know, these two groups ranked it in the top 15. Then finally swimming -- College students put that down at 30. Experts ranked it at 10. Why? Because every year there are a number of drownings from swimming

accidents, and that's what drove their decision making.

So I think this study very nicely shows some of the challenges that you have confronting you with regard to how people perceive risk. Again, in Gideon Koren's paper he talked of this issue of misperception. I think it relates to this, again this fear of the dread, the catastrophic potentials, and sometimes the uncertainties since we don't have a lot of data about these drugs.

Next slide, please. So in summary, determination and communication of risk is a highly complex task, even when you have the best data. There does not appear to be one best method for risk communication.

As you can see, patients tend to differ in what they want. Physicians have a hard time using these expressions, particularly the quantitative expressions. The qualitative expressions are not grounded in any well known quantitative frequency.

Third, perception is critical to the understanding of the impact of risk on the population.

Okay? It's something that needs to be addressed. We also know the errors are very common. Next slide, please.

Well, what is the relevance to drugs labeling? I would sum it up with these three challenges. The first is how do you provide information that effectively communicates the nature, degree and probability of the potential dangers from drugs in a concise, understandable and accessible format? Doesn't seem like too large of an order to me.

Second, a large degree of uncertainty, because as Sandra pointed out, you know, 60 percent of your drugs are in Category C. There's a lot we don't know. You know, how do you deal with this in order to accomplish this?

Then finally, there is substantial dread over possible outcomes. Patients and physicians really do worry. Having worked with a consultative service with the high risk obese at a previous hospital on our consult service, I can tell you, this comes up a lot.

You know, we worried a lot about this. You really don't want to be the one that has something bad happen to your patient. You know, given this and this, it's a real tough combination when you're talking with patients when you don't have data. It's hard enough when you do.

So I hope this has at least given you some backdrop to think about some of the complexities involved in risk communication and some of the challenges. I'd be happy to answer any questions. Thank you.

CHAIRMAN GREENE: Thank you very much, Dr. Holmboe. I'd like to ask you to stay at the podium, and I'll take the Chair's prerogative to ask you the first question or two, please.

You touched briefly on the issue of notoriety of an adverse outcome. An aspect of that is sort of the familiarity of the potential adverse outcome.

So, for example, most patients can relate to the idea of a congenital malformation that they may have seen that's not terribly uncommon, but they have

a lot of difficulty, for example, relating to the problem of pulmonary hypertension from Phen-phen, which may be something they've never heard of.

How do you help patients to understand risks related to possible medical problems or outcomes that they may have never heard of?

DR. HOLMBOE: I think that's one of the major challenges. You know, first off, one thing is that do they understand exactly what that outcome means? I think that's the first step. You know, when you talk about pulmonary hypertension, do they really understand what pulmonary hypertension is.

Again, trying to put that in language that they understand can be very challenging, because they don't understand it. What do you mean, I have this high blood pressure in my lung? I think that's the first challenge.

If you can't get over that first hurdle, you know, then it makes it very difficult to then ensue in a risk discussion, because somehow they've got to be able to grapple onto something that makes sense to them. So I think that's the first step.

Then the second step is that I think what a lot of people are beginning to believe, although we don't have a lot of work on this yet, is that you probably need to present the risk information in several formats.

You need to probably give it to them in several formats and find out what's most accessible to them and kind of query them on several levels: Does this make sense to you? Do you understand what your risk is? But I think, third, you're still stuck with the issue that you're trying to apply population based data to a single individual.

Ultimately, I think understanding their value system and the culture they are coming from is going to have to play a big part in it, because it's very hard sometimes to apply that data, particularly when the risks are very small, because you saw one of the big problems is this kind of compression where we tend to overestimate small risks. It's hard not to.

You know, in medicine we tend to think of a one to two percent risk for a procedure as being fairly significant. A perfect example would be

carotid enterectomy where, you know, the risks from surgery are about two to three percent. That, to us, is important because, you know, the benefits are no better than two to three percent.

To patients, that's a small number. I mean two out 100, you know, they think of 100 people. Two doesn't seem like very many. I think it's real tough to overcome that.

So I wish I had a better answer for you. I think the first step is that they have to understand what the outcome is, and sometimes I find that's very difficult.

CHAIRMAN GREENE: And one other question, if I may. That is the idea that you again touched upon which is sort of a personalization of a risk estimate. Frequently I'll find myself counseling a patient, and I'll think I've done a brilliant job of explicating the risks with quantitative estimations of risk of things that may occur very rarely, and then the patient will sum up the session by saying, well, what have you seen or, you know, what happened to the last case of this you saw. How do you handle that

sort of personalization of the information?

DR. HOLMBOE: I think you bring up a very important point. There's a really nice article. I wish I could remember the author's name, but it was published a couple of years ago in the Hasting's Center Report, and it really focused on this whole issue of how our informed consent has evolved.

The author's point was -- and I think it gets to what you're saying -- that we've gotten to the point where we feel that it's become just our responsibility to provide them with lots of numbers and, if well tell them everything bad that can happen and give them all the numbers, we've done our job.

Then I think you get, you know, exactly what happens to your patient. Listen, doc, I need some help here; I am not the expert. I did not go to medical school; I don't have a PhD in statistics. You know, what do these numbers mean?

This argues for the fact that you don't want -- that, you know, having a little bit of maternalism or paternalism is not necessarily a bad thing as long as you keep it in context that you are

the one with the information. You need to help them put it into context that's useful for them, that simply providing a bunch of numbers and outcomes is oftentimes not very useful to the patient.

In many respects, that's what our informed consent discussion has become. The angioplasty patients I talked about -- they all have informed consent the morning of the procedure, not a real effective time, if you think about it, for them to digest and process information and decide, oh, maybe I really don't need this procedure, because it's only for symptoms. Right?

So, you know, I think that's kind of the evolution. I think you highlight that really nicely. So I think you do have to offer some of your expertise and say, yes, here's been my experience, because the local experience is important.

Again, going back to the carotid enterectomy trial, one of the first things those authors said, you have to know what your local experience is before you can make a recommendation.

So I think it is important to tell them

what your experience has been.

CHAIRMAN GREENE: Are there other questions, first for Dr. Holmboe, and then we'll open it up to the rest of the speakers for the morning. Please?

MS. CONOVER: Beth Conover. I'm a genetic counselor, and genetic counselors are really interested in how we talk about risk. So that was a wonderful presentation.

DR. HOLMBOE: Thank you.

MS. CONOVER: Although I hate to lump, many of the people that we talk to about pregnancy risk are women, and there's beginning to be a little bit of information in genetic counseling literature at least about women perceive risk differently than men, hear risk differently, use numbers differently.

I wonder what your thoughts were on that.

DR. HOLMBOE: Yes. I mean, my background has been in medicine. I haven't looked a lot at the genetic stuff, which I think is fascinating. But all I can say is that, yes, again it does seem to be different just the way this information is processed