UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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RISK COMMUNICATION ADVISORY COMMITTEE

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March 5, 2018
8:30 a.m.

FDA White Oak Campus
Building 31, the Great Room (Room 1503)
10903 New Hampshire Avenue
Silver Spring, MD 20993

PANEL MEMBERS:

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DAVID M. BERUBE, Ph.D.	Member
JOSEPH N. CAPPELLA, Ph.D.	Member
W. TIMOTHY COOMBS, Ph.D.	Member
NATHAN F. DIECKMANN, Ph.D.	Member
ELIZABETH HOWLETT, Ph.D.	Member
GARY L. KREPS, Ph.D.	Member
CHARLES LEE, M.D.	Member
ANDREW PLEASANT, Ph.D.	Member
RAJIV N. RIMAL, M.A., Ph.D.	Member
PAUL SLOVIC, Ph.D.	Member
JEANNIE SNEED, RD, Ph.D.	Member
MICHAEL S. WOLF, M.A., M.P.H., Ph.D.	Member
MYLA GOLDMAN, M.D.	Temporary Member
ANNE LYERLY, M.A., M.D.	Temporary Member
CATHERINE SPONG, M.D.	Temporary Member
JAMES TRACY, D.O.	Temporary Member
ALMUT WINTERSTEIN, RPh, Ph.D., FISPE	Temporary Member
ELIZABETH A. JONIAK-GRANT, Ph.D.	Patient Representative
GERARD NAHUM, M.D., FACOG	Industry Representative
SUZANNE B. ROBOTTI	Consumer Representative
LEE ZWANZIGER, Ph.D.	Designated Federal Officer

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Senior Fellow
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M E E T I N G

(8:00 a.m.)

DR. BLALOCK: I'd like to call this meeting of the Risk Communication Advisory Committee to order.

I'm Dr. Susan Blalock, the Chair of the Committee. I am a professor in the Eshelman School of Pharmacy at the University of North Carolina Chapel Hill. By training, I am a behavioral scientist with expertise in medication risk communication.

So I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I'd also like to add that the Committee members participating in the meeting today have received training in FDA laws and regulations.

For today's agenda, the Committee will hear presentations as background for discussing three issues: first, how information in labeling under the Pregnancy and Lactation Rule is being perceived and used by healthcare providers and other stakeholders; second, factors that are critical to healthcare providers' interpretation of the data and counseling of pregnant women on the risks and benefits of a medication; and, third, how to convey risk information to healthcare providers to accurately and adequately inform risk-benefit considerations for medication use during pregnancy.

Before we begin, I would like to ask our distinguished Committee members and FDA staff seated at the table to

introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. And I'll start with Dr. Lee.

DR. LEE: Hi, my name is Charles Lee. I'm a senior advisor for health literacy and language barriers at First Databank. My area of expertise is in health information technology and access for language.

MS. ROBOTTI: Hi. My name is Suzanne Robotti, and I am the Founder and President of MedShadow, a not-for-profit, and also the executive director of DES Action, an organization for those exposed to diethylstilbestrol.

DR. DIECKMANN: My name is Nathan Dieckmann. I'm an associate professor at Oregon Health and Science University and a research scientist at Decision Research. I study risk communication, judgment, decision making, and biostatistics.

DR. BAUR: My name is Cynthia Baur. I'm a Professor of Health Literacy at the School of Public Health, University of Maryland, and I focus on health literacy.

DR. BERUBE: I'm David Berube. I'm a Professor of Science Communication at North Carolina State University. I co-direct the Research Triangle Nanotechnology Network, and I study risk communication as a social scientist.

DR. SPONG: I'm Cathy Spong. I'm an obstetrician/gynecologist, maternal fetal medicine subspecialist. I'm the Deputy Director of the Eunice Kennedy

Shriver National Institute of Child Health and Human Development. I'm also the Chair of the federal Task Force on Research Specific to Pregnant Women and Lactating Women.

DR. KREPS: I'm Gary Kreps. I'm a Professor of Communication and Director of the Center for Health and Risk Communication at George Mason University. I study the dissemination of health information, particularly for promoting health equity.

DR. NAHUM: Good morning. My name is Gerard Nahum. I am a Vice President of Clinical Development at Bayer Pharmaceuticals. I am a gynecologist by training, and I am here today to represent the industry as a whole, not Bayer individually.

DR. SNEED: Good morning. I'm Jeannie Sneed. I'm a retired professor and department head from Kansas State University and currently a consultant. My area of expertise is food safety, particularly in the retail environment.

DR. WINTERSTEIN: Good morning. My name is Almut Winterstein. I'm Professor and Chair in Pharmaceutical Outcomes and Policy at the University of Florida. I'm a pharmacoepidemiologist by training, and I'm also chair of the Drug Safety and Risk Management Advisory Committee to the FDA.

DR. WOLF: Hello, I'm Michael Wolf. I'm a Professor in General Internal Medicine and Geriatrics at Northwestern University's Feinberg School of Medicine, and a lot of my work

is focused on medication safety and adherence.

DR. RIMAL: Good morning. I'm Rajiv Rimal. I'm a Professor of Public Health and Chair of the Department of Prevention and Community Health at George Washington University. My background is in health communication.

DR. YAO: Good morning. My name is Lynne Yao. I'm the Director of the Division of Pediatric and Maternal Health at FDA. I'm a pediatric nephrologist by training.

DR. NGUYEN: Good morning. I'm Christine Nguyen. I'm the Deputy Director for Safety with the Division of Reproductive, Urologic, and Bone Products, and I am an obstetrician/gynecologist by training.

MS. DUCKHORN: Good morning. I'm Jodi Duckhorn. I'm the Director of the Risk Communication Staff here at the FDA. Thank you all for being here.

DR. TRACY: Jim Tracy. I'm an associate professor at the University of Nebraska, in pediatrics. I'm in private practice in Omaha. I also serve on the Pulmonary Drug Advisory Committee for the FDA.

DR. JONIAK-GRANT: Hello. I'm Dr. Elizabeth Joniak-Grant. I'm here as a patient representative. My areas are chronic daily migraine, arthritis, fibromyalgia, and chronic pain. I'm a sociologist by training. I'm with -- my focus is with qualitative research, talk and interaction in social institutions and people processing institutions.

DR. CAPPELLA: Good morning. Joseph Cappella from the Annenberg School for Communication at the University of Pennsylvania. My work focuses on messages and their effects, both pro and con, both in the health communication area, specifically with regard to tobacco control and other forms of substance abuse. And that's about it.

DR. HOWLETT: Hi. I'm Elizabeth Howlett. I'm a professor at Washington State University, and I'm trained in judgment decision making, and my research focuses on information disclosure within the context of consumer health and welfare issues.

DR. SLOVIC: Good morning. My name is Paul Slovic. I'm a Professor of Psychology at University of Oregon, and President of a research institute called Decision Research. And I work in the field of psychology of risk in decision making.

DR. LYERLY: I'm Annie Lyerly. I'm a professor in the Department of Social Medicine at the University of North Carolina at Chapel Hill. I'm also a research professor in OB/GYN, and I co-direct at the Center for Bioethics. I'm also trained as a general OB/GYN. My research is focused on ethical issues around inclusion of pregnant women in biomedical research.

DR. PLEASANT: Andrew Pleasant, recovering academic, now working in nonprofits, Health Literacy Media and Canyon Ranch Institute. And it says I know something about health literacy

and health communication, so I'll take that as true.

DR. GOLDMAN: I'm Myla Goldman, and I'm a consultant to the CNS Advisory Committee for the FDA. I am an Associate Professor of Neurology at the University of Virginia. My area of practice and research is in multiple sclerosis, Phase II/III clinical trial development, and outcome measures.

DR. COOMBS: My name is Tim Coombs. I'm a Professor of Communication at Texas A&M University, and my area of expertise is crisis communication.

DR. ZWANZIGER: Lee Zwanziger, Risk Communication Staff. I'm the Designated Federal Officer for this meeting.

DR. BLALOCK: Members of the audience, if you haven't done so already, can you please be sure to sign in on the attendance sheet that's located on the table outside of this room?

And Lee Zwanziger, the Designated Federal Officer for this Committee, will make some introductory remarks.

DR. ZWANZIGER: Thank you, Dr. Blalock. I'll now read our FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the Risk Communication Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Except for the Industry Representative, all members and consultants of the Committee are special or regular government employees subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Committee who are special or regular government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of the 18 U.S.C. 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants/cooperative research and development agreements; teaching, speaking, and writing; patents and royalties; and primary employment.

For this meeting, the Risk Communication Advisory Committee has been expanded by temporary members from other advisory committee members -- committee meeting -- I'm sorry,

from other advisory committees, as shown in the meeting roster. Except for the Industry Representative, as noted above, these individuals are special or regular government employees who have undergone the customary conflict of interest review and have received the materials to be considered at this meeting.

These appointments were authorized by Rachel Bressler, Deputy Director, Advisory Committee Oversight and Management Staff.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. 208.

We'd like to remind members and consultants that if the discussions involve any other products or firms not on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Before I turn the meeting back over to Dr. Blalock, I'd like to make a few general announcements.

Handouts for today's presentations are available at the registration table outside the meeting room.

The FDA press contact for today's meeting is Sandy Walsh, who is waving back there. Thank you. Members of the press, please sign in at the sign-in sheet located at the registration table.

I would like to remind everybody that members of the public and the press are not permitted in the Committee area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Committee meeting has concluded.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak, and always use your microphone.

The restrooms are outside and all the way around the hall.

And, finally, let's all silence our cell phones and other electronic devices.

Thank you.

DR. BLALOCK: Thank you.

So we'll start today's meeting with opening remarks from by Malcolm Bertoni, who is the Associate Commissioner for Planning and Director of the Office of Planning.

MR. BERTONI: Good morning, everyone. And thank you very much for being here. As I was just -- I just also want to welcome the members of the expanded Advisory Committee and to our guest speakers and to members of the audience.

As noted, I am Malcolm Bertoni. I'm the Associate

Commissioner for Planning in the Office of the Commissioner. The Risk Communication Staff, which supports this Advisory Committee, is one of several staff divisions in the Office of Planning. We work collaboratively to provide objective planning, analysis, and program evaluation services to improve FDA's policy and performance.

And one of our duties is to support strategic planning and key initiatives around the Agency. And I wanted to take a moment this morning to highlight for you the fact that the Commissioner has published, in January, a 2018 Strategic Policy Roadmap. And it outlines a number of important policy initiatives and actions that the Agency is going to be taking in the coming year.

They generally fall under these four priority areas that are shown here:

- Reduce the burdens of addiction crises that are threatening American families;

- Leverage innovation and competition to improve healthcare, broaden access, and advance public health goals;

- Empower consumers to make better and more informed decisions about their diets and health, and expand the opportunities to use nutrition to reduce morbidity and mortality from disease; and

- Strengthen FDA's scientific workforce and its tools for efficient risk management.

And you can see because I've highlighted in red -- very subtle -- that one of these is actually very explicitly and directly related to the mission of this particular Advisory Committee, empowering consumers to make better and more informed decisions about their diets and health. But I'm sure you would agree that when you think a little deeper about each one of these different areas, the work of this Committee really does affect all of them.

You know, we think of this in terms of the fact that we have an agency that is a science-driven public health regulatory agency. We can harness the best science and make the best decisions, yet if we falter when we communicate the findings and decisions to the public and practitioners, we jeopardize reaping the benefits of all the good work that came before.

And, of course, that's where you come in as an advisory committee. Advisory committees generally play a critical role in getting the best and most up-to-date scientific advice to the FDA and in providing an external perspective on FDA's scientific questions and challenges. You help us improve our understanding of the science and best practices around the complex interdisciplinary fields of risk communication and health literacy.

So I did also want to take a few minutes to highlight some of the accomplishments of this Committee, given that we are now

witnessing our 25th meeting that has occurred over the past 11 years. I remember, and I think Lee remembers when the Committee first started back in 2008. We were here. And I think there has been a lot of important contributions that this Committee has made over the course of this time.

One of the things that the Committee often does is evaluate particular programs. You can see the history there of supporting the Consumer Updates, MedWatch. You, as a Committee, have also driven us and helped us with our strategic planning in this particular area. There was the Strategic Plan for Risk Communication back in 2009. And more recently, there was an update. We added health literacy; it's the Strategic Plan for Risk Communication and Health Literacy.

The first one we called SPRC. And since we added health literacy, we now call it SPRCHL, since we love our acronyms in the government.

But I also have a little thumbnail sketch of another important contribution, in terms of putting the science of health communication and risk communication out there. There is this publication, *Communication Risks and Benefits: An Evidence-Based User's Guide,* that's available on the FDA website. It's a great compendium of different articles from committee members and other experts, and I highly recommend it to anyone interested in this field.

Of course, there are many other contributions. The

Committee has advised lots of different projects and initiatives around the Agency. The Committee especially helps us as we strive to empower consumers, patients, and healthcare providers with information to make well-informed choices about using products to improve their health and the health and well-being of their families.

This Committee often works with experts from other advisory committees, as you are today. A special welcome and thank you to the members joining us from the Advisory Committees for Arthritis Drugs, for Bone, Endocrine and Urologic Drugs, Peripheral and Central Nervous System Drugs, Pulmonary and Allergy Drugs, Drug Safety and Risk Management, and also members from the National Institutes of Health.

This slide summarizes some of the wide-ranging topics the Risk Communication Advisory Committee has worked collaboratively to address across the FDA. I'm not going to read them all. You can read them yourselves.

Finally, welcome to what I have no doubt will be another exciting and informative discussion that will benefit the U.S. public.

So now I will turn the podium over to Dr. Yao.

DR. YAO: Thank you, Mr. Bertoni. My first comment will be that for all of you that are sitting on this side of the room, feel free to turn your backs on the speaker. I know that the room is configured in a somewhat awkward fashion, but we do

want to make sure you're able to access your notes or computer, so we have the screens in front of you. And for the audience, you should be able to see from any of the screens in the room.

But I know, I will not and I would encourage the other speakers not to take any offense if our Committee members on this side of the room turn their backs. Thank you.

Okay. So on behalf of myself and Christine Nguyen and the Planning Committee, I just wanted to provide some opening remarks. I just would also like to say, full disclosure, Christine and I flipped a coin. I won the coin toss, so I get to present the welcoming remarks.

As Mr. Bertoni mentioned, you know, the FDA is involved in many activities, and I thought it would be important just to review for the Committee members the important mission of FDA and many of the things that we are involved with on a day-to-day basis in terms of the protection of health of the citizens of this country.

As you can see, we are one of the oldest U.S. consumer protection agencies, and we are responsible for protecting the public health in many, many areas. One of the areas I want to highlight is that we also have now recently, in the last 5 years, become involved in the regulation of the manufacturing, marketing, and distribution of tobacco products. That is not going to be a focus of today's meeting, nor will the focus be on the regulation of devices. We are interested to hear about

our communications on prescription drug and biological products.

The other thing I'll point out is that we regulate over a trillion dollars' worth of products, which is about a quarter of all consumer spending in the United States. So the work that you have in front of you in the next 2 days, we feel like is critically important in making sure we are absolutely getting the message out the best way that we can.

This is the problem with messaging sometimes, and I also want to point out that, you know, with the beauty of the internet, you call pull up things like this, you know, very easily. And sometimes it's not so clear what the truth is.

Here, I think we have a couple of examples of things that are really out of bounds and pretty easy to tell where the truth lies or doesn't lie. But in many cases, it's very hard to communicate facts in a way that we hope that consumers and prescribers can understand them.

One of the facts that we are trying to communicate when we approve a drug is that it's gone through a review that is very specific in terms of demonstrating effectiveness and safety. And so for your review, I wanted to just briefly go over what the FDA does before it approves a product, a prescription product on the market.

It must demonstrate for that product, substantial evidence of effectiveness and clinical benefit. And that means that it

has a meaningful effect on how a patient feels, functions, or survives, or it can improve or delay progression of a clinically meaningful aspect of a disease.

The evidence that must be generated in terms of making that determination of clinical benefit must consist of adequate and well-controlled investigations so that we can fairly and responsibly conclude that the drug will have the effect that we believe it has been claimed to have. And then, in addition, we must include and review adequate safety information to allow for an appropriate risk-benefit analysis.

Again, as you can see, these are all codified in regulations that FDA is required to follow before approval of a product.

Well, what about approval of a product and pregnant women? So drugs that are approved for adult populations do not require that separate approval is given for that subpopulation of pregnant women. Efficacy, then, that establishes approval in nonpregnant populations supports efficacy in pregnant populations.

Of course, though, we know that dosing and safety can be different, and those data are not always and quite often missing at the time that the product is approved for the general adult population.

It's important to note that pregnant patients who might be taking an approved product have access to that product because

they are an adult patient. And that means that when we're talking about approved products for use in pregnancy, that is not an off-label use. That is an on-label use, but of course, there may be pieces that are missing in terms of the ability to dose properly and to know all the safety.

And then, finally, drugs that are intended to treat pregnancy-specific indications or conditions must follow those same approval standards because these are drugs that are intended to be used in the pregnant population. So I hope I've made those distinctions clear.

Once a product is approved, we, FDA and the sponsor, join in this very elegant dance that I call prescription product labeling negotiations. And the goal of the prescription product labeling is to summarize, as I've outlined on this slide, the essential scientific information needed for the safe and effective use of a drug.

Importantly, the prescription product labeling is intended for the healthcare provider, not for the patient. So there is information available in FDA labeling that can be read by the patient, and that's called a medication guide or patient information that's included as part of labeling.

But the focus of this Advisory Committee, and I want to remind the Committee members, is the labeling that we have written with the prescriber as the focus. However, we clearly understand, and no more place as importantly as during the

pregnancy of a woman, we understand that pregnant women are also consumers of information.

And so we also recognize that patient materials are derived from FDA labeling that can be used for consumers in addition to the prescriber. So we hope that during our conversations today, that we can get advice from you on how to improve on the clear communication of information in this prescription product labeling.

I might also point out the last details, that of course, the product labeling must be informative, accurate, and neither promotional in tone nor false or misleading.

So what about pregnancy-specific information? As I think probably all of you in the room know, that on December 4th, 2014, FDA published a final rule relating to information in prescription product labeling for pregnancy and lactation. And the goal of this rule was to improve the communication of information related to pregnancy and lactation, also to improve on the information we provide related to when pregnancy testing/contraception should be used, and of course, any effects on male or female fertility.

I wanted to let you know that since the rule was implemented in 2015, we have over 500 products now that have complied with this PLLR format. And very soon, in fact, at the end of June this year, we will have a requirement for sponsors to submit products that must then comply with the rule. So you

can see, FDA has been quite busy and will continue to be busy in the next few years with this new rule.

So we've learned some lessons from the first 500 labelings, and we think that we would like to pause for a minute at this point. There's plenty of work ahead for us, and we want to make sure that we're getting it right. And in the places that we're really not quite getting it right, we'd like to hear some advice about that.

So we want to know what's working well, what's not working so well, what improvements can we make, and how are we doing overall? And we would very much appreciate the discussion and the comments here and tomorrow.

So as you've seen the agenda for Day 1, I'm clearly not going to go through this, except to point out that we have assembled, I think, an incredible number of guest speakers with really hundreds of years of experience in the area of pregnancy information communication.

We also have a time for Open Public Hearing, and we have some guest speakers that have spent some time looking at communication of information. So we feel like we've gotten the right people in the room, and we're very anxious to hear the discussion on Day 2. And you can see as outlined, I have generally the discussion outline that we'd like to cover over the next 2 days.

Finally, I'd like to acknowledge the RCAC staff, the

members of the Planning Committee, the members of the RCAC, and also invited members of other advisory committees who are at the table today. And most importantly, I'd like to thank the guest speakers who have made the effort to come and to help us understand where we are today.

The last slide was only to say that the intent of this Advisory Committee is really not so that every child that's born will end up being a princess. But I think it sort of describes the image that every pregnant woman has in their head when they become pregnant, which is to have a healthy baby. And I hope that we can improve on the information we provide so that we can achieve that goal.

Thank you.

DR. BLALOCK: Thank you, Dr. Yao.

And we'll move on to the FDA presentations, and our first presenter is Dr. Catherine Roca.

DR. ROCA: Good morning. My name is Catherine Roca. I'm a medical officer in the Division of Pediatric and Maternal Health. And today I'll be talking about the evolution of labeling information for pregnant women, the pregnancy and lactation rule history and background.

And I'll be starting with a brief background information, history of the Pregnancy and Lactation Labeling Rule, an overview of some of the labeling changes that have occurred as a result of that rule, and some lessons learned along the way.

So just to provide some background, in the United States, there are approximately six million pregnancies every year, and about half of pregnant women report taking at least one medication in pregnancy. And in a study that was done a couple of years ago where they looked at data from interviews of over 30,000 women who provided information about their antenatal medication use, researchers found that on average, women take between three and five medications at any point during pregnancy.

And when they looked across time, because this data was gathered between 1976 and 2008, they found that first trimester use of medications had increased by over 60%, and use of four or more medications in the first trimester had tripled. And I think this really speaks to the fact that we need to have good information in labeling that practitioners can use when they're having these risk-benefit conversations with their patients.

So how did we get to the Pregnancy and Lactation Labeling Rule? This is just a timeline of the history I'll be presenting in the next few minutes, but you can see that this has evolved over a number of years.

In the history of pregnancy labeling, interest in this really goes back to the early 1960s and dates to the thalidomide tragedy that occurred in Western Europe. Thalidomide, as you know, was a medication for insomnia that was being given to pregnant women to treat morning sickness.

And infants who were exposed in utero developed severe limb anomalies.

And this tragedy was largely avoided in the United States because Frances Kelsey, who was a medical officer at the FDA at the time, refused to approve thalidomide in the U.S. because of her concern about the lack of pregnancy safety data.

And on the heels of this tragedy, then Congress enacted the Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act. And as part of these amendments, manufacturers had to prove that a drug was both safe and effective. They had to monitor safety reports that emerged in the postmarketing period, adhere to good manufacturing practices.

And as a result of these amendments, the animal developmental toxicity data increased, and also reports about medication use in pregnancy increased as well. And so by the 1970s, clinicians were really faced with a large body of information, but it was rather unwieldy and difficult to interpret.

And so in 1979, the FDA introduced the Pregnancy Labeling Categories. These are the letter categories that everyone's familiar with. And the idea behind this was to really standardize the presentation of the data and to provide a risk-benefit formula for practitioners.

But, of course, there were some problems with this system. It was overly simplistic, and it was often misinterpreted as a

grading system. And there were also problems in that you could have different levels of risk within the same category.

And just as an example, Pregnancy Category C, which really encompassed the largest number of medications, had two criteria for entry into that category. In one, there were animal reproductive studies that showed an adverse effect on the fetus but no adequate and well-controlled studies in humans, or you could have a drug in Category C that had no data on pregnant women or animals. So within the category, you could have a drug that had adverse animal data or a drug that had no animal data.

And similarly, in Pregnancy Category X, you could have drugs in that category that were known teratogens, or you could have drugs that just had no use in pregnancy, such as oral contraceptives. And so you could imagine a scenario where a woman might be moved from a drug that was effective for her simply to get into a better category, letter category drug.

And outside stakeholders recognized that there were problems with this system. And in 1994, the Public Affairs Committee of the Teratology Society published a position paper entitled, "FDA Classification of Drugs for Teratogenic Risk," and they had a number of recommendations. One was to remove the letter categories in labeling. And the other was to provide narrative statements that summarized and interpreted the data and to provide estimates of the potential for

teratogenic risk.

So the FDA heard some of these concerns from the community and in 1997 held a public hearing with stakeholders to get some feedback about the letter category system. Was it useful? What were the problems with it? And what could be done to improve that statement? And you can see, there are a number of groups that participated in this public hearing and provided input to the Agency.

So FDA took that information and worked to put together some sample pregnancy labeling statements, and they brought those statements to a couple of focus groups that occurred during the 15th Annual Clinical Update in OB/GYN. And these were largely OBs and family practitioners who reviewed these summary statements and provided input to the Agency.

And some of the feedback was that, one, there was a major concern for the lack of human data. Participants were asked, well, if there was no human data, would you rely on the animal data? And the feedback was yes, they'd be willing to rely on the animal data, but it had to be correlated to human dosing.

There was also feedback that labeling statements not be too directive with regards to clinical management, that the most important information for labeling be presented first and that the labeling be uniform across drug products so that it would be easy to locate when someone was meeting with a patient.

In that same year, the Pregnancy Labeling Subcommittee of the Reproductive Drugs Advisory Committee held a discussion and put together a concept paper that really laid out some of the major principles for PLLR. And I just want to recognize that a number of our speakers here today were part of that initial subcommittee.

So taking the recommendations from the subcommittee and the feedback from stakeholders, FDA staff again put together some draft labeling statements and put them to a couple of focus groups, this time with the American College of Nurse-Midwives and the American College of Obstetricians and Gynecologists, and asked them for feedback on these different statements, particularly the risk summaries of the labeling statements.

And the feedback that they got was, again, having some factual statements that then a practitioner could use when they're talking with a patient, but also that it would be helpful in labeling to have a general statement of background risk in the labeling to sort of inform that risk-benefit conversation.

So while the PLLR was being worked on, the Physician's Labeling Rule was revised. And, again, this was another attempt to really try to make labeling useful for practitioners. With PLR though, they did not incorporate changes to the pregnancy and lactation part of the labeling

because PLLR had not been published in its final form.

In 2008 the draft Pregnancy and Lactation Labeling Rule was published, and there was a period of public comment, and the rule was actually revised based on some of the feedback that we received from stakeholder groups and the public.

And then in 2014, the final rule was published and became effective June 30th in 2015. And this really completes the Physician Labeling Rule regulations. And prescription drugs that were approved on or after June 30th, 2001, now have to meet the content and formatting requirements of the Pregnancy and Lactation Labeling Rule.

And then by 2020, all drugs, even those that were approved prior to June 30th, 2001, have to remove the letter category. And as Dr. Yao described, this is being phased in, in a gradual process.

And the intent, of course, is to really provide the prescriber with the information they need to utilize in that decision making with a pregnant or lactating woman, to have a better, more complete statement of the risks based on the data that we have, and also to provide considerations for disease factors that might impact pregnancy as well, for example, diabetes, that has its own inherent risk for anomalies. And this is something that's different, of course, than what was in the previous pregnancy category labeling system.

Animal data have to be put in the context of human

exposure. And, again, this was something that stakeholders were wanting in the labeling. Human data is added when it's available, and if there's no data, that has to be explicitly stated.

So how does the old labeling compare to the new labeling under PLLR? Well, Subsection 8.1, Pregnancy, still exists, but it now includes the data that used to be in the Labor and Delivery subsection. 8.3, Nursing Mothers, is now 8.2, Lactation, and there's a new category, Females and Males of Reproductive Potential.

And this just provides an overview of the different subheadings now with the new labeling. So in 8.1, Pregnancy, if there is a pregnancy registry, that is up top, with the number for prescribers to call. And this again is in keeping with the feedback that we got from focus groups that they wanted the most important information first.

There's a mandatory risk summary; clinical considerations, as I mentioned before, if there are, for example, disease considerations that should be included in that risk-benefit discussion; and then a data subheading and human data, if it's available, comes first and then the animal data.

8.2, Lactation, again has a mandatory risk summary subheading. Clinical considerations, for example, if there's a recommendation to pump and discard milk for after a certain number of hours after exposure to medication, that would come

in that subsection. And then data again, particularly if we have human data from lactation studies.

And then Subsection 8.3, Females and Males of Reproductive Potential, is an optional subsection that would be included if, for example, there needs to be pregnancy testing before a woman is exposed to a medication, if they need to be on contraception while taking a medication, or if that medication has adverse effects on either female or male fertility.

So what have we learned today? Well, it seems that the new format improves the presentation of data. But, of course, it doesn't necessarily help if we don't have data to fill in that labeling. And, of course, the absence of a safety finding doesn't necessarily establish the absence of risk. And so we're working hard to try to more systematically collect post-approval information and to continue to get feedback from our outside stakeholders to modify this process.

And so, in summary, the Pregnancy and Lactation Labeling Rule provides a structured approach to labeling, to hopefully aid in the complex risk-benefit discussions the prescribers have with their patients.

Thank you for your attention.

DR. BLALOCK: Thank you, Dr. Roca.

We've got time for a few clarifying questions. And I'd just like to remind folks that, you know, we've got lots of time for, you know, discussion and making recommendations, you

know, towards the end of the afternoon today as well as tomorrow. So this is the really -- really the spot to, you know, ask any questions to clarify, you know, something that Dr. Roca presented.

Dr. Slovic.

DR. SLOVIC: Thank you.

You mentioned that the absence of a safety finding doesn't necessarily imply the absence of a risk. But what about the presence of a safety finding, say in an animal study that was designed conservatively to make sure to catch any possible effects by giving heavy doses? That may not imply human risk. That's kind of the other side of that coin, but how do you communicate that in a way that might not lead to an overestimation of the risk and unnecessary termination of a pregnancy?

DR. ROCA: That's actually a very good point. Thank you for raising that.

That's absolutely true, that you can have findings in an animal study that don't necessarily translate to human risk. I think that's one of the reasons that stakeholders were so interested to have the animal exposures put in terms of human exposure so that, you know, if you had something that was administered at 100 times the dose equivalent to humans that, you know, you wouldn't sort of overreact and assume that that high dose in an animal would necessarily cause a defect in --

DR. NGUYEN: Hi. Actually -- this is Christine.

I will mention that you're touching the tip of the iceberg, and one of very key reasons why we're convening this meeting today is exactly that. We have very limited data, or we have data that are filled with uncertainties or data that may or may not be applicable to humans.

So, actually, that's the question we're going to ask back to the Panel when we start our discussions of how to communicate these uncertainties.

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thank you. And I want to thank Dr. Roca for a really clear presentation.

My question relates to Slide 19, where you have outlined very clearly the overview of the changes to labeling and the use of specific populations. And I just wondered why, under 8.2, there wasn't a similar place for lactation registries.

DR. YAO: Hi. Lynne Yao. So there wasn't, as I recall, any contemplation with the groups that were formed in the focus groups that described a specific concern about the need for lactation registries. And actually, we have some folks in the room who were actually part of those original meetings.

In my review of the minutes and the papers that came out from those meetings, the large focus was really on the ability to collect information in registries post-approval for outcomes in pregnancy.

DR. SPONG: May I just suggest that that be considered?

DR. BLALOCK: And I have a fairly long list of folks who have questions. Let me just remind folks that the point of the questions for right here are really to clarify something that Dr. Roca presented. And so, you know, you might ask, you mentioned during your presentation, X, Y, and Z, could you please clarify?

So the next person I have on my list is Dr. Lee.

DR. LEE: Okay. So on Slide 12, in the 1999 focus group, there was concerns about being too directive in clinical management. Could you clarify what those concerns were?

DR. ROCA: Sure. There were a number of different labelings that were given to the focus groups. And some of those labelings were more directive about what a practitioner should do with the information. And there was concern, I think, from the groups that, you know, that impinged on practice of medicine, which changes more rapidly sometimes than the labeling would, and that really having factual statements would be most helpful.

DR. BLALOCK: Dr. Nahum.

DR. NAHUM: Yes, thank you.

I have a question that's referable to Slide 12 that you presented. You have a statement there that says I'm "willing to rely on animal data if there was correlation to human dosing." I wondered why you're, you know, pegging this only to

essentially PK and exposure aspects, because it's well known and there was a draft guidance document from FDA with regard to toxicology that tried to, you know, look at correlations between different sorts of species and the REPROTOX data that comes from them and their correlation with humans. And I think, as we all know, that data is very, very inconsistent.

So I guess what I'm asking is, you know, it's not just a human dosing issue that needs to be sort of managed; it's also a human effects issue. And we all know that rats aren't just small people, and same for lagomorphs and others. So how is that being incorporated here? And how is it that we're accounting for the fact that there are basic physiologic differences and metabolic differences between the species we use for evaluating teratogenicity in animals and its correlation with humans?

DR. YAO: So let me just say that the issue of the bullet point was really to encapsulate the conversation that what animal data really even made sense, if any, to include in labeling. And there were those who might have made the argument that there are no animal data that are appropriate to incorporate in labeling, and those on the other side who said, anything we've done, because we did those studies, should appear in labeling.

So part of that bullet was intended to describe the conclusion that was come up at this meeting, to say that, well,

if we are going to include anything, it should have some relevance to the dose that is being used as an approved dose. So that was just to sort of bring down or narrow the conversation in labeling.

There is no question, as you rightly point out, that the animal toxicology data fall very short in terms of their applicability in certain situations to human physiology. But that's, again, part of the issue that we'd like to discuss today. And also, as Cathy pointed out, an important focus of this labeling rule was that we recognize that animal data will qualitatively fall short in many respects, and that when we have human data, we really need to emphasize the fact that we have human data.

DR. BLALOCK: Dr. Goldman.

DR. GOLDMAN: Hi. Yes. Thank you.

I just -- general comment: One, as someone, as a practicing neurologist, not sort of at the edge of this, I think this is incredibly important work and that tremendous strides have already been made in the efforts that have been put forward. My question relates more to understanding the scope of what needs to be done. Specifically, will all FDA-approved drugs -- so this timeline that you have in Slide 7, does that include or is that inclusive of all approved -- oh. Slide -- or maybe it was the earlier, the 2018, 450 projects, 2019. Maybe it was Slide 7 from an earlier

deck.

But my question is will every drug that's currently approved be relabeled? And then to follow on that, has there been any thought to how or in what order they will be relabeled? What is the prioritization of labeling? For example, will it be by sort of grouping or class, like all biologics or all biologics under a certain --

DR. ROCA: It's on page 2.

DR. GOLDMAN: I guess it's four slides above the princess.

DR. ROCA: Oh, from Dr. Yao's presentation.

DR. GOLDMAN: Yeah, sorry. But maybe either one of you could speak to this. But just to understand the scope of what needs to be done, how it will be done, and how this rolls out, as you've outlined. I apologize that it wasn't specifically to your talk.

DR. ROCA: Sure.

DR. YAO: So Cathy has put up a slide here that maybe describes it a little bit better. One of the things that's important to note is that the prescription product labeling that are subject to this rule are only those that must comply with the overall Physician Labeling Rule.

So that's regulatory speak for if you see a labeling that has highlights, that new kind of labeling, as opposed to the first section that says, you know, precautions, it's those new labelings that have highlights. That's new, the new Physician

Labeling Rule format. Any labeling that's currently in that format must comply with the PLLR.

And we've estimated, again as you saw in that slide, that we have about 1,500 or so labelings that will require to fall in that format. But you also rightly point out that any product that was approved prior to 2001 that hasn't come in for a new, you know, condition, a new indication, does not need to comply with this. And there's still quite a few labelings that don't have the update, not just for PLLR but for the entire labeling.

We have thought very hard at FDA about how we deal with those products and how we can update them when it's really important in that the information in those products is very out of date.

In terms of the process of prioritization, we will talk about that a little bit, but it's a little bit off of scope. But there, the rule requires us to update certain products based on the time table. So that's how that grouping originated.

But within those groupings, we are asking our review divisions with CDER and CBER to look at the products that really maybe we need to focus on first, because there's information that really do, you know, really requires update. Or, in fact, we might need to delay a little bit because this will affect many products in a class, and we want to make sure

that we do it all at one time and get the information out rather than just piecemeal but, you know, in a coordinated way.

DR. GOLDMAN: Can I offer a suggestion to that, in follow-up to maybe look at products where there's a specific population target, so, for example, you know, multiple sclerosis where, you know, 90% of the population are young women of child-bearing age, or Crohn's, or where you have biologics, but to look at also sort of the population of the drug, not just sort of Tylenol that may affect every woman, if that makes sense. Thank you.

DR. BLALOCK: I've got two more folks on the list. And then just to keep us on schedule, I think we need to move on to the next speaker.

So Dr. Lyerly and then Dr. Slovic.

DR. LYERLY: Thank you.

I just wanted to leap off of Dr. Slovic's concern about uncertainty around the absence of data and actually go to Slides 4 and 5 from Dr. Yao's talk.

And I think it would be helpful, if you could, just to hear a little bit more about the thinking around the approval of drugs for adults, indicating that the drug is okay for pregnant women because pregnant women are adults, and that being contrasted with the pregnancy-specific requirements just for drugs that are only used in pregnancy, and how you think about that in the context of the different physiologies and

safety profiles that pregnancy introduces.

DR. NGUYEN: So I think that's an excellent question to call out distinction between the two paradigms. So I'll address the easier one, where we're considering approving a drug for a pregnancy-specific condition such as preeclampsia.

So, for that one, we obviously follow the evidentiary standards that were laid out, so it has to be studied in the population that it's indicated for, and certainly this is only pregnant women. So, in those development programs, you are going to have the full spectrum of efficacy and safety only in pregnant women, because that's who it's indicated for.

As far -- so that's an easy one, because in the labeling, you're going to have all the information you need to use in pregnant women.

For other drugs, say antihypertensives, you know, antipsychotic drugs, those really are what we're struggling with, because when we approve a drug in adults, it is really all adults; people with renal impairment, people with hepatic disease, and pregnant women are considered a subgroup of adults from a regulatory perspective.

But we certainly recognize, and that's why the reason we're here, is that there are big gaps in data. And as Dr. Yao pointed out, it's dosing and safety in pregnancy. So the law doesn't say you need to establish that in pregnancy before pregnant women can use it. So that's what we're kind of

struggling with, and that's what we're hoping to obtain more data on.

DR. SLOVIC: We were told earlier that the labeling is for the provider and not for the patient. In Slide 17, where it had the intent of the PLLR, it says again, "Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women."

I'm a little puzzled by the kind of separation of, you know, the design of the label because I assume that the prescriber will rely on this to communicate to the pregnant woman. And it seems to me that there could well then be a disconnect with the language in the PLLR not optimized for communicating to the pregnant woman.

And I wonder if that has been, you know, thought about, taken into account, if actually there has been testing to see that even though the labeling is not designed for that, that if that labeling was used to communicate to a pregnant woman, that it would be maximized for understanding, clarity, and help in decision making.

DR. NGUYEN: So I think this is another area that can get a little confusing. So the prescribing information is really -- the target audience are prescribers. And so the language that's used in there, certainly you would use a lot of scientific terms that may not be readily understandable by the public, you know, the consumers.

And the intent of the PI, that's the acronym for it, is really to provide all the scientific information that's necessary for the prescriber to counsel the patient. So, again, just because the PI is really built towards that target audience, we -- it would be too much of a challenge to try to combine too many target audiences for that document.

Now, that said, there's a lot of information that's based on the PI that then gets translated into more user-friendly language in a medication guide or a patient information leaflet or other sources of information. So the PI is the foundational information, but it is written in more scientific terms and towards the prescriber, and that's who it's intended for.

Now, if a consumer goes to a PI and reads it and can understand it, that's fine. But, certainly, it wouldn't be tested for consumers.

DR. BLALOCK: Thank you.

Before we move on, Dr. Howlett, did you have a quick question?

DR. HOWLETT: Yes. Actually, this was just following up on Slovic's. My quick question was just a point of clarification, which was when in the decision process would exposure to this information be presented? And sort of following, would the consumer then be exposed to the same sorts of information that the prescriber is presented?

DR. NGUYEN: So what the consumer is exposed to, the type

of information, is somewhat channeled by the prescriber who's counseling her. And certainly -- never mind the internet and all the third sources of data. But, certainly, there are information in the prescribing information which is very comprehensive that may not really be germane to the consumer and for which she may not see -- for example, mechanism of action, it may not really be relevant to her decisions to use the drug, whereas it might be important to the prescriber to understand the efficacy of the drug.

DR. BLALOCK: Thank you.

So thank you, Dr. Roca.

And let's move on with the FDA presentations. Our next speaker is Dr. Leyla -- is it Sahin?

DR. SAHIN: Good morning, everybody.

So I'm going to be talking this morning about fulfilling the intent of PLLR. I'm going to be presenting FDA's current approaches and challenges.

The objectives of my talk are to provide an overview of the data sources that are used to inform labeling. I'm also going to be talking about the challenges in terms of how we get from the data to labeling, and I'm going to be illustrating these challenges with some examples of labeling that we have worked on and have approved.

Where do the human data come from? Pregnant women are mostly excluded from drug development trials in the effort to

protect the developing fetus from an investigational product. Because of this, data on safety in pregnancy are collected in the postmarketing phase. And the data can be found published in the medical literature or the data can be submitted by pharmaceutical companies who either fund or conduct pregnancy safety studies.

I'm going to start off by talking about pregnancy registries because they are the most common type of pregnancy study required by FDA as a postmarketing requirement. Pregnancy registries are prospective observational cohort studies that compare outcomes in pregnant women who have been exposed to a drug with a cohort of pregnant women who have not been exposed to the drug.

Advantages include the prospective design of the study and the detailed patient-level data that can be collected, including confirmation of outcomes based on medical records and based on adjudication of outcomes by a clinical teratologist.

Disadvantages include the small sample size, because we know that it is challenging to recruit and enroll women into these studies. There's also selection bias.

In 2014 FDA held a public meeting on pregnancy registries where we heard from Dr. Lew Holmes, the Director of the North American Antiepileptic Drug Pregnancy Registry, that women who enroll into pregnancy registries tend to be highly educated and of a higher socioeconomic status. So there's concern that

these studies may not be representative of the general population.

Retrospective cohort studies are also being commonly required by FDA as a postmarketing requirement. These studies are based on administrative claims or electronic health data. Advantages of these types of studies include the large sample size.

Disadvantages include exposure misclassification because exposure is based on pharmacy dispensing. So we don't really know if the woman actually took the drug. There may be outcome misclassification because outcomes are based on diagnoses codes, which tend to be nonspecific. Non-live-birth outcomes are not typically assessed, and so we're missing birth defect data in spontaneous abortions, pregnancy terminations, and stillbirths.

Case control studies are often conducted by surveillance networks, like the CDC's National Birth Defects Prevention Study, which is now in its second phase called BD-STEPS, or the Vaccines and Medications in Pregnancy Surveillance Systems case control study, the Birth Defects Study, and we'll be hearing more from a VAMPSS representative in the next talk, or from state-based surveillance networks.

Because these are population-based data, these studies provide the advantages of having a large sample size, where there's sufficient power to assess specific rare birth defects.

Disadvantages include the recall bias, because sometimes women may be interviewed about their drug exposure up to 2 years after they've had their delivery. And because there are multiple statistical comparisons that are conducted, we tend to see chance findings.

Pharmacovigilance data are case reports, what we refer to as spontaneous reports that are reported to FDA's Adverse Events Reporting System. Pharmaceutical companies also maintain a database of these reports that include both normal and abnormal outcomes.

Advantages of pharmacovigilance data include that they may facilitate early signal detection if there's a clustering of a specific type of birth defect or a pattern of birth defects.

Disadvantages include the unknown denominator, which means that we don't know the total number of women who were exposed to the drug, and so you can't really come up with an accurate rate of birth defects or other adverse outcomes. There is often important information that's missing, such as the timing of exposure, the dose information, use of concomitant medications, comorbid conditions, and specifics on the outcomes. There's also reporting bias, because abnormal outcomes tend to be reported more frequently than normal outcomes.

In terms of how the data are assessed, this involves a multidisciplinary review that includes pharmacoepidemiologists,

medical officers with expertise in maternal health and separate medical officers with expertise in the disease area, and biostatisticians.

Factors that affect the ability to draw conclusions include the quality of the individual studies that were conducted; the consistency of findings across studies, especially in studies that use different methodologies or designs; the sample size of individual studies, but also the cumulative exposures in pregnancy -- so are we talking about a few hundred women who were exposed to the drug, or are we talking about thousands of women; power considerations of the various studies that were conducted; the choice of comparator and whether it was appropriately adjusted; whether it appropriately accounted for confounding due to the underlying disease; whether there was adjustment for confounders and biases in the cohorts; whether there's information on the timing of exposure -- with birth defects we're specifically interested in the first trimester exposure; and whether there's dose information because there may be dose-response relationships; and then, finally, biological plausibility, and are the findings in humans consistent with the underlying mechanism of action of the drug and whether those findings are consistent with findings in animal studies.

Challenges with interpreting the data include the limitations of the individual studies. So are there

methodological issues? Are there differences in the exposed cohort compared to the comparator cohort that preclude drawing any meaningful conclusions from the study findings? Small sample sizes: Often studies have insufficient power to show a difference in the outcome. And then differences in the outcomes that were assessed; pregnancy registries tend to look at overall birth defect rates, whereas case control studies look at specific birth defects.

So it's difficult when you have various studies that you're looking at, you're trying to make comparisons across studies. Perhaps the most challenging issue is when we have conflicting study results.

This brings us to the intersection of science, regulations under the PLLR, and then communication of data in labeling. In terms of how we get from the data to labeling, this involves multidisciplinary meetings and discussions where we get together and discuss everybody's assessment of the data. We compare our assessment to the company's assessment. We look at what the company has proposed for labeling, and then we revise and refine the language of labeling based on our assessment and our conclusions.

We spend a lot of time and effort developing the risk summary statements, which is basically the take-home message. Before PLLR, we used to devote a lot of time and effort in determining what the pregnancy letter category was going to be.

Now we focus our efforts on developing the messaging.

In the next few labeling examples, I'm going to present some approved labeling to illustrate some of the challenges that we have encountered.

The first labeling example is to illustrate the situation where we only have animal data, which is common when drugs are first approved. This is Xenazine (tetrabenazine), which is approved for treatment of chorea associated with Huntington's disease. You can follow this labeling example on page 15 of the backgrounder document.

The Risk Summary states that there are no adequate data on the developmental risk associated with the use of Xenazine in pregnant women. Administration to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality.

Administration of the metabolite produced adverse effects on the developing fetus, including increased mortality, decreased growth, and neural, behavioral, and reproductive impairment. These adverse effects occurred at clinically relevant doses.

So we have chosen this example because we are interested in getting input from the Committee on how this information is presented in labeling and what we could do to improve the statements here to make it more useful to the prescriber.

This next slide has the animal data presented in more

detailed information. In the interest of time, I'm going to move on to the next example.

The second example is to illustrate the situation where we have inconsistent study findings. This is Zofran (ondansetron), which is approved for chemotherapy and postoperative nausea and vomiting. And it's important for everybody to note that this drug is commonly used by obstetricians off label to treat nausea and vomiting of pregnancy.

So, in this situation, there were two large retrospective cohort studies that had conflicting findings. One study showed no increase in malformations. The second study found an association with cardiac malformations. There was a case control study that showed an increased risk of isolated cleft palate. There were several small observational studies that had been performed, but they were really too small to detect anything but a major teratogenic effect.

And so this is what the labeling ended up looking like. You can follow on page 22 of the backgrounder. Please note the language that's highlighted in red. Again, we'll be asking the Committee for input on the specific words, the specific language and statements that we've included here.

The Risk Summary reads as follows: "Available data do not reliably inform the association of Zofran and adverse fetal outcomes. Published epidemiological studies have reported

inconsistent findings and have important methodological limitations that hinder interpretation."

Under Human Data, we have additional detail on the studies that were conducted. So one retrospective cohort study that included 1,349 infants who had been exposed to ondansetron because the women had received a prescription in the first trimester showed no increased risk for malformations. However, in a sub-analysis of the study, there was an association with cardiovascular defects and cardiac septal defects.

The odds ratios are included here. Again, we'll be asking the Committee to weigh in on how they feel about the inclusion of odds ratios and whether this is informative for the prescriber.

So the second study included 1,970 women who received a prescription for ondansetron during pregnancy, and there was no reported association with malformations, miscarriage or stillbirth, low birth weight or small for gestational age.

This is followed by a description of the limitations of these studies. So here we see a statement that says that limitations include that we're uncertain of whether women who filled a prescription actually took the medication, we don't have information on concomitant use of other medications or treatment, and there may have been unadjusted confounders that may account for the study findings.

The case control study found an association with isolated

cleft palate. Again, the odds ratio is presented here, and then we see a description of the limitations of the study that says that this could be a chance finding, given the large number of comparisons that were conducted. And then we don't know the exact timing of exposure during pregnancy and whether it occurred during the sixth and ninth week of pregnancy when the palate is formed in the fetus. In addition, the isolated cleft palate has not been corroborated in any other studies.

The last example is to illustrate the lack of a consistent safety finding. This is Enbrel (etanercept), which is approved for various types of arthritis and for plaque psoriasis. So, for this particular example, there was data from a pregnancy registry and a retrospective cohort study that both showed a higher birth defect rate compared to unexposed women with the disease, but there was no pattern of birth defects.

You can follow along on page 24 of the backgrounder. Under the Risk Summary, there's a statement that says that, "Available studies do not reliably support an association between etanercept and major birth defects." Again, we'll be asking for input on this statement.

Clinical data are available from the Organization of Teratology Information Specialists pregnancy registry and a Scandinavian study in pregnant women. Both studies showed a higher rate of birth defects compared to the disease-matched unexposed group of women. However, a lack of pattern of major

birth defects is reassuring, and differences between exposure groups, for example, the disease severity, may have impacted the occurrence of birth defects.

Under Human Data, we have a description of the study, so the OTIS study included 319 exposed pregnant women, with a birth defect rate of 9.4%, compared to the disease-matched unexposed cohort that included 144 women and had a birth defect rate of 3.5%. The Scandinavian study included 344 exposed women, with a birth defect rate of 7%, compared to the disease-matched unexposed cohort that had a birth defect rate of 4.7%.

So this was a challenging situation where the numbers were showing one thing, but our interpretation was different than what the numbers were showing. We consulted the CDC for further input. So Dr. Jan Cragan, who is a birth defects expert with the CDC, did an independent review of the data. And her assessment and her conclusions were consistent with the FDA.

The goal of labeling is to provide information in a clear and concise manner to facilitate prescribing decisions. Our goal is to have balanced messaging and labeling in the context of the background risk. Although every pregnant woman wants a perfect baby, providers and patients need to understand that there's always a background risk of having a baby with a birth defect or having a miscarriage or having other adverse outcomes

that occur.

We also want to have balanced messaging in the context of treatment benefit and not just focusing on the risk of the treatment but also recognizing that there is benefit to having treatment.

And then, finally, consideration for the public health impact and the impact of the labeling information once it gets disseminated to the public.

We do have a concern for potential unintended consequences of labeling. We're concerned about confusing messaging because that would not be helpful for the prescriber. We're concerned about incorrect messaging. If what is presented in the labeling results in a risk perception that's worse than actuality, or worse than the truth, whatever that may be, this could result in unnecessary discontinuation or switching of treatment or pregnancy termination. If what is presented in labeling is perceived, if the risk is perceived as being better than actuality or better than the truth, then this could result in false reassurance.

So the challenges are many. The data, in many cases, are absent. The quantity of data are often limited, and the data themselves often have limitations or there may be conflicting study findings. Because of all these limitations, data to support definitive risk statements are usually lacking. And risk statements that are less than definitive are very, very

difficult to communicate in labeling.

So this is my final slide. In summary, clear and balanced messaging is the goal. The messaging needs to balance risk with the benefit. And hopefully, my presentation has been able to convey to the Committee just how challenging it is to develop labeling and messaging in the presence of imperfect data.

And I'll be happy to take questions. Thank you for your attention.

DR. BLALOCK: Thank you, Dr. Sahin.

And, you know, we are running quite far behind, and so really, you know, just a couple of, you know, brief clarifying questions. And I'm going to actually ask what I think might be a clarifying question.

You know, in several of your slides where you showed, especially where I'm thinking about the risk summary, and you would highlight some things in red, how much of the language in the risk summary is standardized, would be the same for any medication that fell in the same class?

DR. SAHIN: Thank you for your question.

So this is a comment that we've received from stakeholders is that there is a lot of variation in labeling across divisions and across drug products and across disease areas. And so we have taken those comments into consideration, and we have been trying to develop more consistent type language.

So that's why we have highlighted some of that language in red, for the Committee to weigh in on, because that is representative of some of the type of standard statements that we have been incorporating into labeling.

DR. BLALOCK: Thank you very much. And we'll have lots of opportunity to weigh in, you know, later this afternoon and tomorrow.

I saw Dr. Cappella.

DR. CAPPELLA: Just a question of information.

Obviously, the research on pregnant women and the consequences of any particular medication is going to change over time. How frequently are vendors expected to update the labeling, or is the FDA updating the labeling? And what are the chances that that information is going to make it to prescribers?

DR. SAHIN: Thank you for your question.

That was one of the major intents of PLLR, is for the updating -- for the labeling to be up to date and not outdated the way it used to be prior to PLLR. It is really the responsibility of the pharmaceutical companies to keep on top of the medical literature and follow the medical literature and then revise the labeling as appropriate.

So we don't have -- we haven't developed a specific schedule, but that is the FDA's expectation, that this responsibility falls on the companies.

DR. BLALOCK: And Dr. Baur has a question, and then we'll move on.

DR. BAUR: Thank you, Dr. Blalock. I wanted to ask a follow-up question to yours.

So just in the examples that were provided in the presentation, I counted at least five different versions of these statements about data. So there's no adequate data, available data do not reliably inform, preclude a reliable evaluation, no clear evidence, and available studies do no reliably support. That's five different ways of saying things that I don't even know if they're the same or not.

So I'm wondering, could you just clarify, are you asking for feedback on those variations, or are you saying that they reflect the different terminology that the review teams as chosen, as when they do these evaluations?

DR. SAHIN: So we tried to pick three labeling examples where the amount of data or the available data, there were differences. So the first example was a situation where there was only animal data and no human data. So we have specific types of language that we've been using in those scenarios. And then the second example was when there was inconsistent study findings, and then the final example was where we were basically reassured with the data that we didn't think that there was an increased risk for malformation.

So I don't know if that provides some clarification,

but -- so the language is -- there are nuances, and there are differences and variations in the language for different scenarios.

DR. BLALOCK: Thank you, Dr. Sahin.

DR. SAHIN: Thank you. Thank you.

DR. BLALOCK: And we're going to go ahead and push back the break. You know, we've got a break scheduled at 9:30, but we're going to go ahead and push that back. So we'll move on to our guest, the guest speaker session. And our first speaker is Dr. Jennifer Namazy.

DR. NAMAZY: Hello. I just want to thank everybody for inviting me as one of the speakers today. I'm an allergist/immunologist at Scripps Clinic in La Jolla, but I'm here on behalf of the American Academy of Allergy, Asthma and Immunology, and specifically the Vaccine and Medication during Pregnancy Surveillance System.

And so I'm eager to present to you some new data from a survey that we provided to our membership on the implementation of the new PLLR, to give you some feedback.

I have no conflicts. And Dr. Roca and Sahin did a great job in terms of reviewing the new PLLR, which came into effect in 2015, and with the goals of providing prescribers with relevant information for decision making when treating pregnant or lactating women. And so I hope that this survey data will help you as well.

As a clinician, I had several questions, and we took it to the team to create this survey, but these specific questions were: Were physicians aware, first of all, of the change to the PLLR, and how comfortable were physicians with the new PLLR format? And were clinicians reverting to the previous pregnancy letter category system? And were clinicians finding the necessary information meaningful for their critical decision making in caring for this special population of patients?

So, in collaboration with the American Academy of Allergy, Asthma and Immunology -- this is a professional organization with over 7,000 members in the United States, Canada, and 72 other countries. This membership includes allergists, immunologists, other medical specialists, allied health and related healthcare professionals, all with a special interest in the research and treatment of allergic and immunologic diseases.

This is a pilot survey that was released in the beginning of this year. We sought to obtain information on demographics, such as age, type of clinical practice, and we also sought to determine awareness of the new PLLR, understanding of a sample narrative summary, and the value of the new PLLR in terms of day-to-day practice.

In terms of demographics, 1,500 members received an email invitation to participate in the electronic survey, and this is

about 33% of the U.S. membership; 126 practicing allergists responded. Sixty percent were in single and group multi-specialty organizations, the rest were in academic and private practice. Sixty-five percent were male, and the median age was 56 years. And this also gave us an idea of how long these clinicians were in practice.

In terms of awareness, by asking the following questions, we were able to assess whether the new PLLR was being used and how often.

So the first question was are you aware that the pregnancy letter categories A, B, C, D, and X on prescription medication labeling are being replaced with narrative summaries of the risk of using a medication during pregnancy? Fifty-six percent of all responders were not aware of the new PLLR changes.

When asked how often do you use the medication labeling to obtain prescribing and safety information for your pregnant patients, 86% use the medical labeling to obtain prescribing and safety information.

And when asked, on average, how many pregnant women do you prescribe medications to per month, responders prescribed, on average, medications to two pregnant women per month.

I'm sorry that this is so small, but this is the sample narrative summary that was presented to those survey takers. And this was for a hypothetical drug, ABC, used for moderate to severe persistent asthma. And it is a monoclonal antibody. I

just wanted to highlight that this medication does have a pregnancy exposure registry.

And then under Risk Summary, the data on pregnancy exposure from clinical trials were insufficient to inform on drug-associated risk. There was information on animal data, and there was information on disease-associated risk, specifically poorly controlled asthma having potential adverse perinatal outcomes.

Then the responders were shown this and asked how much do you agree or disagree that the narrative summary labeling of drug ABC is clear and concise? Forty-nine percent of responders felt the narrative summary was clear, and twenty-nine percent felt the narrative summary was concise.

There were several comments -- there were a lot of comments, but these are a few, that it was unclear and impossible to use, on a busy clinical day this is a lot of reading, and it was hard to interpret this information.

They were then asked do you have experience referring pregnant women to a pregnancy exposure registry? Only 25% had experience. But after reading the information about the pregnancy exposure registry for drug ABC, 54% of responders were likely to refer their pregnancy patient to the registry.

When asked how helpful or unhelpful background risk information and disease-associated risk information was to the responder, 73% of 120 responders found the background risk and

disease-associated risk information to be helpful. And when asked about how helpful or unhelpful was animal data, 65% of responders found animal data to be helpful.

In terms of assessing the value, having seen the narrative summary, we asked, overall, how helpful or unhelpful is the narrative summary labeling for drug ABC compared to the pregnancy letter category A, B, C, D, and X that used to appear on drug labels?

Sixty-two percent of responders found the narrative summary, compared with previous pregnancy categories, to be unhelpful. Comments: "It will lead me to prescribe less medications to pregnant patients," "too complicated."

When asked how often do you use the pregnancy risk letter categories A, B, C, D, and X instead of the narrative summary to make prescribing decisions for pregnant women, 76% of responders used the pregnancy risk letter categories instead of the narrative summary. Comments were "Quicker and easier to use," "easier for patients to grasp."

And when asked, overall, do you think the new labeling has brought more and meaningful information to you and your patients compared to prior labeling, 57% of responders felt that the new labeling did not bring more meaningful information to them and their patients.

And after reading the narrative summary for drug ABC, 63% were unsure if they would prescribe the medication, and some of

the comments were, only after a thorough discussion regarding the risk and benefit with the patient would they consider doing that.

So, in conclusion, the goal of the new PLLR is to bring a more complete statement of the known risks based on the available data. This survey provides a first look at the impact of the new labeling. The majority of responders did not know of the new PLLR changes. Most responders were reverting back to letter categories when counseling patients.

Most of the responders found the risk information included in the labeling to be helpful. More than half of responders felt that the new labeling did not bring more meaningful information to them or their patients, that compared with past letter categories was unhelpful.

I just wanted to have a couple of slides. There were several comments in regards to navigating narrative summaries on multiple medications in a busy clinical practice. And I just wanted to stress that ambulatory care, over the last decade in the United States, has been struggling and had a lot of challenges, specifically with maintaining cost effectiveness all the way to transitioning to an electronic health record.

This study was performed by the American Medical Association to try to quantify how much time was spent by physicians in ambulatory care. And rather than provide a survey form, to avoid bias, they actually sent out people to

observe 57 physicians across specialties.

And what they found was that 27% of time was spent on direct patient care, while 49% of time was spent on electronic health record and desk work. And while in a room with patients, only 50% was spent direct face-to-face. And the mean time spent with a patient across specialties was about 20.8 minutes. And for every hour spent with a patient, there was 2 hours of desk work and computer work. And this has led to some unintended consequences, such as physician burnout and poor patient communication.

Also, comments were about being less likely to prescribe medications for pregnant patients. And one of my areas of interest is the treatment of allergic disease and asthma during pregnancy. It's one of the most common chronic medical problems to affect pregnancy. And we know that poor asthma control during pregnancy leads to adverse perinatal outcomes.

And one of the big barriers to control, unfortunately, is clinician undertreatment. One study showed that of pregnant asthmatics presenting to the emergency room with acute asthma, only 38% were discharged on oral corticosteroids. While in the ER, only 50% were treated with systemic steroids versus 74% of nonpregnant asthmatics.

In another study, because of the perceived risks of corticosteroids, over a quarter of family physicians have said they would instruct their pregnant patients to decrease or

discontinue asthma medications during pregnancy when asthma was well controlled with current therapy, in this case being inhaled corticosteroids.

So what's next? Based on this survey, the new labeling is not meeting the perceived needs regarding prescribing during pregnancy of a majority of responding allergy/immunology clinicians. Many clinicians still do not know of the new PLLR labeling changes. Many clinicians lack the time to navigate through information and present it in a clear way to their patients.

Continued education of clinicians of the new PLLR changes is essential, and I hope we will continue to use this survey among clinicians from all specialties as a tool of understanding and value of the new PLLR.

I'll take questions.

DR. BLALOCK: Thank you, Namazy.

Any brief clarifying questions? Dr. -- is it Robotti?

And, again, please remember to say your name, and this is for the transcriptionist, so that they can have a complete transcript.

MS. ROBOTTI: I'm Suzanne Robotti.

At the beginning of your talk, you said you had no conflicts of interest, but this slide here says Conflict, Advisory Board, Genentech. Just a clarification.

DR. NAMAZY: Which is not in terms of what I'm presenting

today.

DR. BLALOCK: Dr. Goldman.

DR. GOLDMAN: Just maybe to expand or I think you touched on something really important as an allergy specialist versus a family practitioner versus the obstetrician. And I think one of the challenges or things maybe to keep in mind, and I'd be interested in your thoughts, is who's reading the information, who's communicating to the patient, and how do we begin, or should we take that into account in thinking about this issue, in terms of pregnant women with chronic disease?

Do they need to see a specialist? Is the obstetrician interpreting it? Who's interpreting this language for these individual women?

DR. NAMAZY: You know, that's a really great question.

I mean, I can only speak as an allergist/immunologist, but I think it affects everybody. I think it affects everybody, all clinicians that are going to be taking care or managing this population of patients, for sure. But I would like to see -- like I said, I would like to see this go across all specialties. I think we'll see similar.

DR. BLALOCK: Thank you very much, Dr. Namazy.

So I think it is time for a break. And looking at my watch, I think maybe we can at least try to cut it a little bit short and come back promptly at 10. And, you know, please remember not to, you know, speak to folks outside about the

material that's being discussed here.

(Off microphone comments.)

DR. BLALOCK: Oh, okay. And I'm reminded, you know, the most important stuff is the food. So if you haven't ordered lunch, be sure to try to do that during the break as well. Okay. I'll try to come back at 10.

(Off the record at 9:46 a.m.)

(On the record at 10:00 a.m.)

DR. BLALOCK: So if I can ask folks to find their spots. And I will call the meeting back to order. And our next speaker is Dr. Michael Greene.

So Dr. Greene.

DR. GREENE: Yes. Thank you. Thank you so much for inviting me. Dr. Sahin, thank you for the invitation. I appreciate it.

And without further ado, these are my disclosures. These are other entities that pay me for work I do other than caring for patients. I don't believe that any of them represent a conflict of interest, but they're all here for your perusal.

This was my charge from the Committee: Four points, please address these four points. And I will try to address these four points in my remarks this morning.

So with respect to what's been my experience with the labeling of drugs for use in pregnancy and lactation, in fairness, in 1998 I was an SGE, and I was a member of the

Reproductive Drugs Advisory Committee. And at that meeting, in my first meeting in 1998, Sandra Kweder, who had been tasked with leading the charge for changing labeling in pregnancy, asked me if I would chair a subcommittee that would start to address the issue of labeling and pregnancy.

From 1998, these were the original three tasks that she charged us with as a subcommittee. And in fairness, it was the easiest job I ever had because Sandy actually did all the work. And over the next several years, she and I consulted back and forth together. She would come up with ideas of how she would like to rewrite the label. She'd run them past me. We'd chat about them. And so I kept in touch with the effort through her in that way over several years.

And in 2005 I convinced her to come to Boston to tell the Obstetrical Society of Boston where the effort stood. And as they sometimes say in the military, Sandy was overtaken by events, OBE, because right before she was scheduled to come to give this talk in Boston, she was designated by the FDA to explain to Congress what happened with Vioxx and why so many people had heart attacks.

So she didn't make it. She sent me her slides, and I was sufficiently familiar with what was going on, I gave her talk for her from her slides. So that's my involvement, and I would just like to bring a few issues to the attention of the Committee from the background document that was released as

part of the final rule, which were comments that the FDA received. And these will mesh with some of what you've just heard from the previous speaker.

One comment suggested that depression should not be treated pharmacologically during pregnancy, whereas a separate comment suggested that the FDA ban the use of all drugs and vaccines during pregnancy.

The FDA received 16 comments from physicians, pharmacists, pharmacy associations, nurses, manufacturers, drug and safety consultants, etc., etc., that they retain the category system or replace it with a similar system, with another standardized schema.

To the credit of the FDA, they said that experience and stakeholder feedback has taught them that pregnancy categories were heavily relied upon by clinicians but misinterpreted, misunderstood, and erroneously used as a grading system, where fetal risk increased from A to X.

At the risk of singling out one child that is your favorite, the part of the pregnancy labeling rule that I think is most important is this, which is the requirement that the label be updated. That was always a serious problem with the label. There is absolutely no incentive -- there was no incentive for a manufacturer to update the label.

The number of pregnant women that are going to use any one medication generally is relatively small compared to the

overall market for the drug, and the perceived liability on the part of the manufacturer is much too great to encourage their use during pregnancy.

So this requirement that the label be updated when new human data concerning the use of drugs, of a drug during pregnancy becomes available, if that information is clinically relevant, FDA believes it is necessary for the safe and effective use of the drug, and therefore the pregnancy subsection of the labeling must be updated to include that information.

Previously, the only updates that were required were basically the infamous black box warnings, if there was a known severe adverse effect. But if it was shown to be benign, there was no requirement to update the label to that effect.

The FDA believes that it is necessary for the safe and effective use of the drug, and therefore the pregnancy subsection of the labeling must be updated to include that information. Failure to include clinically relevant, new information about the use of a drug during pregnancy could cause the drug's labeling to become inaccurate, false, or misleading.

So with respect to how we counsel and approach counseling patients with respect to use of a particular drug, I thought it would be useful to go through the one, a single example, the use of lamotrigine, which is an anticonvulsant, was originally

approved by the FDA for the use as an adjunctive therapy in patients with partial onset seizures in 1994.

Over the course of the lifespan of the medication, it received additional labeling indications, as indicated here, such that now there are a relatively large number of indications, including as a "mood stabilizer," quote/unquote, in certain disorders, psychiatric disorders, specifically bipolar disorder.

But the main use is still as an antiepileptic drug. And this is a survey from the European Union, "Use of Antiepileptic Drugs in Europe." And you'll notice that between 3 and 6 patients in 1,000, pregnant women in 1,000, will be treated with an antiepileptic drug during pregnancy.

And it's hard to argue that these women do not need to be treated or can just stay off of their medications during their pregnancy with no adverse consequences. I don't have to go into the details of what could happen if somebody had a seizure under the wrong circumstances. So it's important to treat women. The new holistic approach is just inappropriate.

And this is data just from two of the countries that were cited in this study -- there were several countries, as you saw on the original slide -- comparing which drug, carbamazepine or lamotrigine, was used most commonly. And you'll notice that lamotrigine had grown into very common use as the most common in many of the Nordic countries especially.

As mentioned already this morning, pregnancy registries have become an important part of the risk assessment apparatus that has been required by the FDA over the years. And this, when you go to the FDA's website, the first one that pops up actually is the one on antiepileptic drugs, which is a multiple-drug registry that's actually based at Massachusetts General Hospital and run by Lew Holmes. His name has also been mentioned previously.

And a paper published in *Neurology* in 2008 found a very alarming risk, an increase in risk for cleft palate with the use of lamotrigine in pregnancy based upon a total of three exposures amongst 680 -- or rather, three cases among 680 exposed, for a relative risk of 21, with a lower confidence bound of 6.8.

You might say gee, 21, that looks pretty bad. How could that possibly be wrong? Well, in fairness, in that same publication, Lew did recognize that other studies had found lesser risks of cleft palate.

And several years later, 4 years later, published again from the same database, this time by Sonia Hernandez Diaz at the Harvard School of Public Heath, using Lew's database, wrote that "We published a risk of oral clefts of 7.3 per 1,000 among 684 users of lamotrigine monotherapy. With a larger sample of 1,500, the estimate's now 4.5 per 1,000." The lower confidence bound was still 2.2, but other studies have -- and she

acknowledges that other studies have reported lower risks of oral clefts after first trimester lamotrigine exposure.

So if we had been counseling a woman about the risk of lamotrigine in pregnancy in 2009, we would have to tell her that there was a 21-fold increase in risk of cleft palate at that time, and 4 years later, we'd have to say whoops, well, maybe not. Okay.

So this is part of the problem of counseling patients with imperfect information. And, in fact, this illustration, this figure from Sonia Hernandez's paper in 2012, shows that except for gabapentin, which looks almost protective, lamotrigine had the lowest risk of all birth defects of all of the anticonvulsants studied.

This is a subsequent meta-analysis that appeared very recently, and I know the print is small. That's why I gave you the big red arrow here, showing the comparative risks for all major congenital malformations. The big red arrow is lamotrigine, and you'll notice that it falls right on the line of unity. That's for all major malformations.

For all causes of fetal loss, again, lamotrigine falls right on the line of unity. For comparative risk for intrauterine growth restriction, lamotrigine falls right on the line of unity. And here, for risk of preterm birth, lamotrigine again falls on the line of unity, suggesting that, in fairness, this looks like among the safest drugs to use for

treating epilepsy during pregnancy.

Now, despite that fact, okay, the label for lamotrigine in March of 2015 still read as follows: "There are no adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine has developmentally toxic," etc. When lamotrigine was administered to pregnant rats and mice, it made them sick. To provide information regarding the effects of in utero exposures to lamotrigine, physicians are encouraged to encourage their patients to call the registry.

So I would suggest, as mentioned a few minutes earlier this morning, that although not false, this label is misleading, okay, because it's inadequately updated with the latest information.

As far as principles for counseling, I would say that questions that we ask and we go through with patients when we're treating them is, first of all, how important is the medication during your pregnancy? Again, in this case, lamotrigine, if you need it to control your seizures, it's hard to argue that you don't need it and we can just discontinue it.

If needed, could the medication be suspended during organogenesis? That's always been the main concern since the days of thalidomide, as discussed earlier, is major birth defects. However, we do know that there are adverse effects that can occur from medications later in pregnancy, but with respect to major organogenesis, at least the question could be

asked, could the medication be discontinued during the first trimester?

It's important to look, as we mentioned, as I mentioned with the example of lamotrigine, not individual birth defects but overall all birth defects, and it's terribly important to emphasize the difference between relative risk and absolute risk.

And a relative risk of 1.5 for left ventricular outflow tract defects associated with an SSRI exposure would not be a blip in the overall 2.5% risk of congenital malformations. So the relative versus absolute risks must be discussed with the patient.

There are potential fetal risks of in utero drug exposure other than classic birth defects, and we know about those problems, neonatal abstinence syndrome with opioids and benzodiazepines, for example.

And, finally, discuss the quantity and quality of the data available to address the various risks, especially confounding by indication. We don't give medications to people at random. We give medications to people who are at risk for problems. We don't give insulin to people who don't have diabetes, for example. And diabetes in and of itself is associated with a substantial increase in the risk of major congenital malformations.

The impact of medicolegal environment is undeniable. This

is a website that is very easy to find on the internet, of course, a website that was accessed just right before coming to this meeting, right before I had to submit my slides.

This law firm advertises, you know, if you're on Lamictal and something bad has happened, call them up and they'll help you with your case, making a case that the birth defect, whatever it was -- they're not discriminatory here -- whatever the birth defect is, they're happy to help you sue your doctor and the drug manufacturer presumably.

What can we do with respect to the legal environment? There's not a whole heck of a lot we can do, other than be very assiduous about our documentation. Frequently, I will print not usually the label, to be perfectly honest, but usually what I'll print is the summary of risk from either TERIS or REPROTOX, which are standard reproductive databases that have sort of bite-size nuggets of information that patients can more readily understand.

And, finally, what is it that OB/GYNs want in labeling? Well, it's the modern era. Ideally, whatever we have, it should be internet-based, not a PDR that's 4 inches thick in paper on your shelf. It should be internet-based so that both physicians and other care providers, nurses, nurse practitioners, and others who are in positions to have to counsel pregnant women, as well as pregnant women can access the information themselves.

They may or may not understand all of the information, but it's a good starting place to bring to the doctor to facilitate the discussion. I believe that it would be best if this was publicly available and not behind some sort of a pay wall or a firewall, that it needs to remain current, and the data must be evidence-based and reliable.

And, finally, on my wish list would be that the label, the official label, which as you all know is an official document, a government document that is agreed to by the FDA and the manufacturer, that that be given some dominant expert opinion in a court of law and not equally weighed with an expert who is an expert by virtue of being a pediatrician in private practice in Florida for 40 years, which is what happened with Bendectin, for example.

So those are my thoughts. That's my wish list, and I'm happy to answer questions.

DR. BLALOCK: Thank you, Dr. Greene.

Do any members of the Committee have a brief clarifying question?

Dr. Nahum.

DR. NAHUM: Yeah. No, no. I have a question about one of the things that you said, that sponsors are typically slow to update their labeling. And I think that, you know, that's -- I think you meant to say that they're slow to update the labeling with regard to evidence of increased safety because it's clear,

I think, that most sponsors are more than predisposed to try to incorporate into labeling adverse events that are associated with exposure to medicines, just from a medicolegal perspective.

So my question is if that's the case, what would be your threshold for sponsors being able to say that they essentially could prove a negative? In other words, how many exposures would be necessary, and what would be the comparator group to be able to say there's no increased risk or minimal increased risk from a clinically important different standpoint for a sponsor to have to update a label to say that a product is safe during pregnancy?

DR. GREENE: Yeah. That's a really good question, and actually, that was a question I was going to ask of the folks of the FDA later in this meeting, which is safety, as we all know, is relative. And if no problem shows up in 3,000 people in the Phase III trials, which is sort of a standard size of most Phase III trials -- there was a great editorial years ago by Abby Lippman-Hand in *JAMA*, the title of which was, "If Nothing Went Wrong, Is Everything All Right?"

Okay. And the problem is a zero numerator. Okay. So you're absolutely right. A good example is fen-phen. Okay. There was no evidence that fen-phen caused any problems during the Phase III trials. And it wasn't until it was marketed and hundreds of thousands of people took it that we recognized what

the problem was, and the FDA had to take it off the market.

So it is relative and relevant. But safety is relative. In fairness, Allen Mitchell wrote a very nice editorial in the *New England Journal of Medicine* some years ago, saying that with X number of patients, if nothing happened, much like Abby Lippman-Hand pointed out, you can say pretty confidently that the risk is no greater than Y. Okay.

So yes, you can calculate the upper 95% confidence bound for a zero numerator. It's not really that hard. So rather than saying the available data does not permit any calculation, you can say that the available data suggests that it's no greater than, at worst, the 95% upper confidence bound. So --

DR. BLALOCK: Thank you, Dr. Greene.

And moving on to our next speaker, Dr. Katherine Wisner.

DR. WISNER: Thank you very much for the invitation to present here today.

I'm going to give you my perspective as a perinatal psychiatrist. And my talk is entitled, "Prescribing for Pregnant Psychiatric Patients: Progress Report," bit of alliteration here.

So one of the things that I was asked to do is to talk about the public health significance of psychiatric illness, and I'm going to focus on depression in pregnancy; secondly, to talk about factors that influence patient acceptance in a risk-benefit type of decision-making process; and lastly, comment on

what psychiatrists want to see in labeling.

Depression has huge public health impact. According to the World Health Organization, it's a leading cause of disability in women worldwide. We know that the lifetime prevalence of depression in women is about 1 out of 5, 21%; for men, 1 out of 8; which means that in this room, there are many of us who have or will have depression.

The pregnancy-related death rate in the United States has increased across the last three decades, and one of the contributors to the increase in that death rate has been self-harm, particularly suicide in post-partum depressed women. So, again, this is a major public health problem, with relevance specifically to the pregnant population.

When I do this kind of talk, I worry that we talk about depression in the abstract, you know, that it's a disease with a bunch of symptoms. But I wanted to bring in a poem that one of my patients wrote, to talk more specifically about what this feels like, to lose your ability to engage emotional tone, to feel positive emotion, so that what you're left with is negative emotional affective states.

And I think, in this poem, where this woman who is pregnant says, "You say I'm carrying life inside; how can that really be? How could life possibly survive in a nonexistent me?"

So the ability we all have to temper what happens in life

with positive things that happen is lost. It's an inability in the brain to feel those positive affective states.

When a woman has one episode of depression, her risk for another increases. So with one episode, you have a 50% to 60% chance of having another episode. If she has two episodes, it's more like 70%. And if she has three episodes, the rate is more like 90%, which means that her depression is likely to be chronic, and maintenance treatment may be required to keep her well.

The other thing that we do in psychiatry, the other goal is to treat that patient to remission, not just response, like we targeted several years ago, which would be a 50% reduction in symptoms, but a good clear remission, asymptomatic, not having any symptoms. That's because we know that if she has residual symptoms, the risk for relapse is much higher.

In pregnancy, we know that the risk of having depression carries a number of obstetrical and neonatal risks that we are all concerned about. So the disease of depression is associated with higher rates of these negative outcomes in pregnancy. And we all worry about preterm birth, C-sections, low birth weight. Again, these are all associated with depression, which is associated with maternal stress and maternal lifetime experience of stressful events, such as trauma.

The other area that we're concerned about with depression

is that this woman who bears this child provides the primary caretaking experience in most families, when a woman with depression is the one responsible for the milieu, the environment that this baby is born into.

In my world, which is a psychiatric specialty clinic, we see many women like this woman on the couch, where the ability to manage her own emotions is so dysregulated, her ability to manage a newborn, where her job is to try and move that newborn to either sleep or to alert comfortable state, that's really her job. If she can't do that for herself, she can't for the infant.

And that is how that infant learns regulation, is through that primary caretaker and her or his ability to provide that, that sense that the environment is responsive, out there to help, available. And the lack of that kind of early experience creates the difficulties you see on this slide under long-term impairments, which include behavioral problems and, down the line, social deficits.

So how big a problem is this? Several years ago I did a study in which I evaluated 10,000 women from Magee-Women's Hospital in Pittsburgh. And what we did was we offered women who delivered at that hospital a screening for depression by phone at 4 to 6 weeks postpartum.

So we did our screenings with the EPDS, which is a standard screening measure for depression. And what happened

was the delivery staff there worked after hours, met with the women who delivered, talked about depression, gave a pamphlet, and offered our screening. Again, the vast majority of women accepted that screening by phone at 4 to 6 weeks postpartum.

At that time, our screening staff, who were trained to give this administration by phone, the EPDS by phone, called those women by phone and gave them the screening. If they screened positive, which was an EPDS score of 10 or more, which is a relatively low threshold, if those women screened positive, we offered them a home visit, at which time they got a full psychiatric assessment, evaluation, feedback, and referral.

At that screening visit or at the initial screen, at 10 or more, 14%, 1 out of 7 women in this large population of women screened positive on the EPDS measure. The more typical cutoff point in clinical populations is 13. At that cut point, 7% of the population screened positive. And what you see is a typical distribution of scores for a screening measure, where the majority are screened negative, but depending on your cutoff, you know, some degree of women screen positive.

We also did those home visits, as I told you about. And at those visits, we asked these women, when was it that the illness that you screened positive for began? We found the typical epidemiologic finding, which is that the majority of those episodes start after birth, after the massive withdrawal

of hormones, which seems to provoke depressive episodes in vulnerable women.

So at this 4- to 6-week time period, when we screened our patients, 40% of those screened positive said this began after the birth of the baby. About 33% of our patients said this episode began during the 9-month period of pregnancy. And we had about a quarter of our women say they had this depression even prior to pregnancy, which has led to many recommendations now, many guidelines stating that women should be screened in pregnancy, typically at the first prenatal visit.

In our organization in Illinois, where perinatal depression screening is required by law, they're also screened in the third trimester in addition to that postpartum period.

When we looked at the diagnoses for those women we did home visits, who had careful psychiatric diagnostic assessments, we found what is typically, again, found in epidemiologic studies, that the vast majority of these women have mood disorders, that the primary disorders that are precipitated during pregnancy are depression.

And in our sample of women who had screened positive, we found a very high number of women not only with unipolar or what's called major depression, but with bipolar depression or manic depression. This again is known that the post-birth period is a time for first onset mania/hypermania episodes. Those episodes are indicative of bipolar disorders, which are a

lifetime diagnosis but, again, which are commonly precipitated in that post-birth period.

When I was a resident, I had patients who I was seeing who were pregnant, and I would go to my supervisors and talk about this pregnant woman with depression. I was told that I was wrong. Kathy, women who have depression in pregnancy, they really can't have depression because pregnant women are fulfilled. You must have the diagnosis wrong. This is what I was actually told when I was a psychiatric resident.

It's part of the reason I went into this type of research because it made me really angry to think that women who were pregnant couldn't have this disorder. And, in fact, there is still, in some sectors, a myth that women are fulfilled and that women don't have depression in pregnancy, what I call the myth of protection from mental illness.

In fact, a study that came out from the Harvard group with Lee Cohen as a primary investigator showed that, in fact, of women who discontinued their medication proximal to becoming pregnant, about two-thirds became ill again with a recurrent episode, and about a quarter who maintained their medication became depressed. So certainly this was evidence that significantly more women stayed well when they continued their medication.

However, Dr. Cohen was a little distressed with me because my question to him was why is it that a quarter of women who

continue their medication that's previously effective, why do they become ill? And I'll talk about what I think was happening there a little bit later in my talk.

The other point is that the recurrences emerged rapidly. That is, women who tapered off their medication or, worse, quit suddenly, which we know is related to recurrence, those recurrences again emerged rapidly.

The other point I would make here is that this is an academic, high-risk population. However, we know from epidemiologic data that of women who become depressed, who are evaluated for severity of depression, about half of those women have severe depressions that cause significant disability. So the idea that this is, you know, a minor illness, that women can get by without medication is not true for every patient.

So I'm going to talk now about how I approach risk-benefit decision making. I wrote an article about this, now 18 years ago, but it remains the only comprehensive review of thinking about how does one structure a risk-benefit decision-making process for depression in that time period.

And I do always emphasize the bottom point here. Part of what I love about my work is that the vast majority of these women and babies, the outcomes are very good, very happy, very healthy. That's the rule rather than the exception. And the concern that we have about the risks must be tempered with the incredible benefit that we give by talking about how these

treated illnesses are also important for a healthy pregnancy.

So in our depression treatments, we certainly have non-pharmacologic treatments, and many patients prefer non-drug therapies. I don't mean to go through all of these treatments, but I wanted at least to mention that there are a number of evidence-based treatments for depression, many of which, including the various psychotherapies, for mild to low-level, moderate depression, do have similar efficacy to medication.

But in thinking about why women make certain choices, some women are very adamant that they want to stop their medication in pregnancy, in which case my strong recommendation is not to just stop and see what happens, which happens in the majority of cases, but to taper off medication slowly, set a point at which they would decide that perhaps they need to go back on medication, whatever that is for their particular risk-benefit analysis, and instead of just stopping, to pick one of these other types of interventions which are known to reduce the risk for depression.

Unfortunately, the vast majority of women stop cold turkey, go off and just wait to see what happens. And those are often the women that I see in my practice, much more severely ill, having suffered a recurrence, and perhaps then getting treatment or inpatient admission that require far more pharmacotherapy than the single drug alone.

The study that Allen Mitchell did about the number of

women who take various medications in pregnancy also produced this particular graphic. And because these illnesses, depression, anxiety disorders for which SSRI antidepressants are the drugs of choice, that they occur so often in childbearing-aged women that these medications, the SSRI are often used in pregnancy. And you can see that across time from the '70s through mid-2000s, 2006 to 2008, the number of antidepressants, which is the red graphic, increased dramatically across that time frame.

The graph is a little misleading in that 8% of women were exposed to antidepressants. In this same study, about 2% to 2½% of women continued those antidepressants in pregnancy. And those were likely to be those women who made that choice because they felt as though their risks of not continuing were very high.

Those are the women that I tend to see in my practice, too, where they come in wanting to know about the risks of antidepressant treatment, but many are armed with the benefits, like every time I go off the medication I become suicidal, or my job is compromised, and I lose my job, my insurance, and I'm the only care provider for my three children.

So women have very individualized reasons why they value either staying on the medication, trying to taper. They have very individualized values. And it's not unusual for me to see women with very similar clinical histories, very similar

responses to medication, say I cannot take a drug at all because if something happens, I will have made that choice, and I won't know whether it's the drug that caused it, but I will feel bad, or I absolutely must take this medication because without it I can't function and that's a terrible risk for me.

So, again, I would emphasize that these are incredibly individual decisions that women bring very different values to.

So I would like to talk a bit now about how I structure the consultation. So when I do a consultation about antidepressants or any drug in pregnancy, the first thing that I do is not talk about the agents, but I talk to her about her expectations.

I want to get a sense of her knowledge of pregnancy physiology, what she makes of risks, what her obstetrician, the internet, friends, what they have told her and what she believes about medication exposure, and her understanding of what disease she has and what the exposures from the disease may be.

And Dr. Patel and I did a study of thinking about these decision processes and the preferences and preferences for the way that we interact with patients. And what we -- what I think about in these types of decision-making processes is what does that patient expect of me? And that goes all the way from, tell me what to do, doctor, to I really just want to know these facts, and then I want you to help me understand how to

make that decision for my set of values, which is actually my preferred way to interact with patients.

Then I collect data through the interview. History is very important. I always conduct a standardized measure of symptom severity. That is not standard in my field. Typically, it's an interview and a cataloguing of symptoms. I want to know, by a standardized measure, what level of symptoms she has. Is it mild, moderate, severe? And I think that's critically important for the medicolegal documentation that Dr. Greene mentioned.

Other exposures and documenting those in the record are critical because if there's another exposure that's not documented, but your exposure is and there's a bad outcome, it's the one that is documented that potentially carries the assignment for the risk for that negative outcome.

And then other disease exposures are critically important as well, as well as the course of pregnancy and previous pregnancy outcomes. So I'm looking at all of those different kinds of data when I talk to her.

The other thing that I do is talk about what is my prescription for her treatment, independent of pregnancy. So I don't even think about the pregnancy. I put that over here because I want her to understand, for the disease she has, the treatments that I think are evidence-based, most likely to lead her to a good disease-reduction outcome. I want her to

understand that first.

And I want her to ask questions about that. I document all those questions. This is a bias that I have towards control of the disease process. Then what I do is talk about here is how I would modify that disease-reduction, disease-control plan because you're either pregnant or contemplating a pregnancy. And sometimes there are no modifications. I also provide the rationale for those modifications for reduction of her disease.

This is a graphic from my paper, more that I just wanted you to have the different types of outcomes that I go through. We focused on birth defects primarily here, but there are a lot of data out there about SSRI antidepressants. And I go through many of the other kinds of outcomes, particularly after I understand what her concerns are. It may not be birth defects, and often it's when my child is in school, will his intellectual function be affected?

A comment about explaining things to patients and to physicians sometimes as well: We've heard about confounding. Explaining confounding to both patients and sometimes to physicians, I think, is critically important, because by and large the internet view is here is an SSRI; exposure to SSRI or any other drug yields this birth defect.

And explaining that what Dr. Greene was talking about, that the SSRIs used to treat a disorder -- and the disorders

that I treat are often confounded with all kinds of psychosocial risks, trauma, domestic violence, neighborhood violence, other kinds of negative events that we know have impact on pregnancy. So explaining what those confounding variables are that go along with the disease for which the drug is used is critically important in these data explanations.

So the final point I would make is when I talked about the idea that a quarter of patients who continued their medication got sick, I think the other thing that's important is if we're going to use a drug, we owe it to our patients to use an effective dose.

There are a large number pharmacologic changes that occur in pregnancy. And we have looked at changes in plasma concentrations across pregnancy, and I want to show you some of those data now. So what you are looking at is fluoxetine, which goes by the common name Prozac, sertraline or Zoloft, citalopram or Celexa.

And what you see is the concentrations in the blood of those agents from 20 weeks through delivery to 12 weeks post-partum. And you see the decline of the primary drugs, which is the bottom lines of those graphics, you see that those decline across pregnancy.

And we commonly see women who suffer recurrences in pregnancy because the enzymes that metabolize these drugs are increased across pregnancy and therefore the efficacy is lost.

So we are now doing a study to determine how commonly that happens, when exactly in pregnancy it happens, and how we can monitor our patients more carefully.

So for the practitioner, what do we want? We've heard some of these recommendations. And I think the other thing that is critically important is more data about disease outcomes to provide a balance to the overemphasis on the risks.

The other idea that I think is important is what physicians don't like is being surprised at the end of a visit with having to provide information about pregnancy. I did some consultation in New York for a while, in their public mental health system. And they had a very interesting idea of preparation to see the psychiatrist.

And what was done was a pre-interview about what do you want to learn from the psychiatrist. And it was a question about are you planning a pregnancy and are you using birth control? And if there was a pregnancy plan, information about the drugs that patient was taking in pregnancy was provided to the psychiatrist as part of the preparation for the meeting.

I think that's a really helpful way to think about a sort of brief preparation as opposed to, oh, gee, what am I going to tell this person? I use the fact sheets from MotherToBaby, the Organization of Teratology Information Specialists, very commonly as a handout to patients. And, again, the documentation, I think, is important.

The other area that we're working on is we assume that prescribers know the basics about pregnancy pharmacology principles, about pregnancy in general. All prescribers are not that savvy about prescribing for pregnant patients. Some people refuse to prescribe at all. And I think we need a pharmacology curriculum for pharmacologists or for people who are prescribing for pregnant patients.

And with that, I'll stop with this slide and be happy to answer any questions.

DR. BLALOCK: Thank you, Dr. Wisner.

Any brief clarifying questions for Dr. Wisner?

Dr. Goldman.

DR. GOLDMAN: Hi. This is Myla Goldman.

Could you speak to looking at that postpartum depression risk and what you know about affective disorders in general, how it relates to decisions to breastfeed or not breastfeed and how that is relevant?

DR. WISNER: Yeah. Okay, so -- oh, wow. A couple of points. First, in our setting, it's a very pro-breastfeeding setting, so that women who typically take medications in pregnancy take them through breastfeeding as well. And for the antidepressants, that's really appropriate. The benefits of breastfeeding by and large outweigh the risks of the antidepressants.

In terms of decision making, we did a study in which we

looked at women's intent to breastfeed at the beginning of pregnancy. And by and large, what we found in this depressed population was that women who stated their intention to breastfeed at the beginning of pregnancy by and large continued to have that intent and, in fact, breastfed.

What we see is that the maintenance of wellness is critically important in helping that woman continue to breastfeed postpartum, so that women who develop depression may assign breastfeeding as one of the reasons that they're not getting to sleep, and they may stop breastfeeding but then find out often that their depression's worse. Not always, but many times that's the case.

And so one of the other things that we've looked very carefully at is what I think about as starting off on a very good path.

So our anesthesiologists have been working with us to be very adamant about controlling perinatal pain well, from the initial epidural through those early postpartum days, and trying to make the patient as comfortable as possible, to encourage breastfeeding, to encourage her use of that emotional availability, to be able to use those skills and that comfort to get off on a good step, in terms of breastfeeding, in terms of attachment. So we're paying a lot more attention to that early postpartum time frame.

DR. BLALOCK: Thank you very much.

I don't see any more questions, so I'd like to invite Dr. Laura Riley.

DR. RILEY: Thank you. Thank you for the opportunity to share my experience.

I'm going to talk a little bit more about vaccines, sort of change gears, and talk some about the ACIP recommendations and how we get to where we get to.

And so in terms of disclosures, I am a member of the CDC's Advisory Committee on Immunization Practices, and I also write for UpToDate.

So I was asked to consider sort of what are the challenges in treating mother and fetus and newborn, and then talk a little bit about the role of labeling and the ACIP recommendations when counseling about various vaccines, and then also to talk a little bit about what factors are prioritized when considering the use of a vaccine during pregnancy or also the postpartum period.

And I chose to use the flu vaccine as an example, just because as it happened, in making the slides, things were happening about the flu, and I thought, well, at least we're all on the same page.

So just as a historical perspective and, you know, I think probably everybody in this room sort of is well aware, I think there's no question that flu is really an important illness, particularly for pregnant women. And in all three pandemics,

1918, 1957, and the obviously, the most recent in 2009, pregnant women did not fare well in the flu season.

And just to remind people, in 2009, the H1N1 pandemic, 56 deaths were reported, and they were reported in all trimesters, although it has been known that the third trimester of pregnancy is particularly dangerous for a bunch of physiologic reasons.

So just drawing a little bit more information from the H1N1 epidemic, I think this is really when most of us said, oh my god, this is really bad. Young, healthy women got sick, so it wasn't women with multiple chronic diseases and pregnancy who got sick. Many of them had no coexisting illnesses, yet they got sick, and many died.

And then the other, you know, major issue that was seen in this pandemic was that a delay in the antiviral treatment, i.e., Tamiflu, led to a greater death rate. So people, women who arrived in the emergency room or on labor and deliveries and clearly had the flu or symptoms consistent with the flu, but there was a delay in treatment or recognition of the disease, those women fared much worse than those who were treated immediately.

So what is the recommendation? Well, the flu recommendation's really pretty clear. It's been around for years now. All pregnant women should receive influenza vaccine every year during any trimester of pregnancy. And as you can

see, besides the CDC, multiple societies, professional societies have been on the same page for years, giving this information, yet sort of where are we?

So I'm going to go back to the CDC, as that was the primary question to me, which was, you know, sort of how does the CDC decide and what do they use to decide on those recommendations? And so this is -- I actually utilized slides that I just saw last month at our CDC meeting.

This suggests that, you know, in -- the ACIP adopted the grade approach in October of 2010, and I'm sure all of you are aware, that really relies on the quality of evidence for benefits and harms, and it assigns a grade to that. And then also, it allows you to go from the evidence to the recommendations.

And the CDC really does look at not so much the package insert but the original information that went into that labeling is basically what we're looking at in the information that's graded. And then the quality of the evidence for benefits and harms is really only one factor in developing that recommendation. So yes, the label is important, but I'd say all of these other things are equally weighed in.

And so because these other factors are included, balancing the benefits, the harms, the values, and health economic data, the CDC has -- or I should say, ACIP has chosen to expand now and go beyond just using grade.

And so this was presented actually at the last ACIP meeting just a few weeks ago. And essentially it's called Evidence to Decision Framework. And it's quite extensive, but it makes the decision making a little bit more transparent to the public and to all of you, about how we go from that original data and all of the information that we incorporate to come up with a recommendation, which is obviously for public health.

So the frameworks are intended to help these various panels. And in this particular situation, the ACIP sort of structured the discussion around times when the data tells us one thing but we're thinking something else, or there is that conflicting data. It allows us to sort of put it all out there on the table.

It also allows us to be much more systematic about how we make recommendations about each individual vaccine. So sometimes, basically the way it's done is, you know, if you're making a recommendation for influenza, the Influenza Work Group looks at primary data. They make a recommendation based on all of those things we just talked about, and they come out with a recommendation.

The work group that works on, say, Tdap then does the similar process, but they don't always present it in the same way. So you're left wondering, how did they come up with their recommendation? Is there a different process? And the whole

purpose here is to use the same framework for each vaccine.

And so this is what it's going to look like essentially, which will be presented from every single work group that comes up with a recommendation on a vaccine. And, really, the purpose of showing it here is to suggest that again, that primary data that goes into the labeling is really only one small piece that is a integral part, obviously, of the recommendations that come out, yet these are all the pieces that come in.

So the statement of the problem, sort of the public health importance, and so for flu I just, you know, showed what the public health importance is, you know, specifically for pregnancy. And then also going through the benefits and harms, I think that that's a really important piece.

And obviously we know, certainly with vaccines, the number one issue in pregnant women's minds is safety. Safety for their baby is the top priority for them, and getting beyond that in a conversation is sometimes very, very difficult.

Also, other things in this framework that obviously aren't taken into consideration is the values and preferences of the target population.

So, again, in pregnancy, considering that there are going to be multiple new vaccines on the market eventually that are specifically for pregnancy, such as, you know, sort of RSV, CMV coming down the pike -- there's others -- the target population

in understanding the values of pregnant women and their preferences is going to be very important in coming up with these recommendations in addition to all the primary data.

Acceptability to stakeholders, as you can imagine, pregnant women are a particular stakeholder group, and they're making decisions for their babies as well as their whole family, which can be particularly challenging. The resource use as well as feasibilities are the other parts of this framework that are going to be considered.

So here's just using as an example flu vaccine, so this is the package insert that I just clicked on the internet and found 2 weeks ago before I put my slides in. And as you can see, Pregnancy Category B, so the categories are still out there on the internet. And it's interesting; there's not a whole lot of data here.

And certainly if you like, just, you know, go down to nursing mothers, it's not been evaluated in nursing mothers. I mean, flu vaccine has been around forever, and we've been giving it to pregnant women during pregnancy, after pregnancy. And the thought that we don't have information is very disconcerting.

So this does translate into issues, right. So when people don't have information, they make different decisions. And so this is just a quick, you know, snapshot of the flu vaccination coverage rates for pregnant women. This is based on the

internet survey that the CDC does yearly. And it looks at -- clearly, the top, the blue line looks at women who were -- their provider suggested to them that they get the flu vaccine.

And it is very clear, and has been shown in multiple studies in addition to the internet surveys, that if physicians or midwives or whoever the OB provider is suggest to a patient that they get the flu vaccine, they're much more likely to get it. And so at that point, you know, more women get it if they're suggested to, but still the coverage rates are around 50%.

And as you can see, the biggest uptick though, actually, which I didn't put on the slide, was 2010, after the 2009 pandemic, when before that sort of the coverage rates were, you know, 14%, 18%. People were not getting vaccinated.

And so this is something that has come up, which is really kind of concerning. And this is again using the internet survey. But this is looking at earlier in 2017, just a quick snapshot, where it looked like way fewer women were getting vaccinated this year than would have been anticipated, only 35%.

So who knows what will happen over the course of the season? This is early in the season. But, you know, many people start getting flu vaccine in late September, early October, so 35% was not a number we were hoping to see.

The question is how do we get there? Like why do we have

these low coverage rates? And I think that it's because there's a lot of factors that go into why an individual woman actually gets the vaccine. So there's the providers. I talked about what our influence is. There are the patients themselves; it's the mothers, the babies. It's their families and their friends who are telling them whether or not this is a good idea.

The sources of information, other people have mentioned it. The internet is, you know, is our friend and not our friend. Interpretation of that information, I think, speaks to all of these different factions. And then the decision itself, and this I was talking to Dr. Greene about last night, I found this absolutely fascinating. You know, we think that we're giving patients all of the information in a way that they can digest it, but actually, it's interesting, this article suggests that at the end of the day, the decision making is actually not even rational.

So, you know, it just makes you pause, right. You think that you're giving all the right information and that people are going to make a rational decision from that, but they don't. But I guess the people around this table, though, have way more experience in that than I do.

So this has been seen multiple times. I think that what is a trick here is that for vaccines that were not investigated, particularly in pregnant women, lots of these

pieces of information that are going to go onto the label are going to be blank. And the question is what do you do in that situation, and how do you frame that, that question -- or those answers, I should say.

So consideration specific to pregnancy, when I'm thinking about vaccine use, and actually, when I'm talking to my own patients, I'm thinking about pregnancy physiology, like what is the impact of the disease I'm trying to prevent?

And pregnancy immunology, you can't just say, nah, it doesn't make a difference. The impact of a vaccine may, in fact, make a difference on the immunology, both for the mother, because it's quite tricky, and then also for her newborn.

And then obviously safety -- huge. That should be in big bold letters. There are, you know, maternal issues, there are fetal issues. I think we have a tendency to talk only about birth defects, but you know, the brain's developing for all of pregnancy, and moms know that, and they want to understand what the impact could be. And then I mentioned the fetal immune response as well.

And then postpartum issues are important, exposure to breastfeeding. Women will make the decision. If you think that -- if you suggest that there's any risk, they're going to make two decisions: Either I don't want to be vaccinated, or I'm not going to breastfeed. Neither one of those are decisions that we are particularly excited about, but this is

what happens.

I do think that it's important for women to understand, and for providers as well. It's amazing how many providers do not understand the depth of the safety system that has been set up for vaccines.

This depth of safety, I would say, has not been set up for all drugs, but it does help us in some situations, in many situations for vaccines. And I think that there's multiple ways in which individual vaccines are later looked at in the public.

And so I just bring this up because there's the good, the bad, and then sometimes there's the ugly. So this is a paper that came out in *Vaccine* earlier this season. It was entitled, "The Association of Spontaneous Abortion with Receipt of Inactivated Flu Vaccine," and it was only in these two seasons.

It was an incredibly tiny number of patients who then went on to have miscarriage. There were a million different ways that this study could be torn apart, yet it got published, and it got some press.

On the flip side, there are multiple other studies that were done, and one even from this same group, which suggested that in fact the flu vaccine is not associated with first trimester miscarriage, and hence the vaccine recommendation that it can be given in any trimester of pregnancy.

So you had one study out there. This was the response to

the quote/unquote "signal," and it was called a signal because there was this question about safety. The CDC tried to get out in front, and that's on your far left, "Flu Vaccination and Possible Safety Signal." And that information was guidance for healthcare providers trying to, you know, put it in some kind of perspective of what this study was, what the findings were.

The study clearly states that it was not causal. But you can imagine, with that title, what it sounded like. And then this is how it played out in the news. *The Washington Post, Stat,* and NBC, I have to say, they did an amazing job at trying to, in addition, give the information but also set up the study such that people -- it was clear that there were flaws in the study that needed to be taken into consideration.

I think the issue, though, is that what you have is -- on the other side is what -- you know, how did the blogs take this very same study, and you know, they turned it into, you know, the flu shot during pregnancy, what is your doctor not telling you? And if you read the details, they go into how, you know, there's yet another study that shows that this isn't safe.

And what's really interesting, and they go on to say, you know, a recent study found that the flu vaccine is linked to an increased link of miscarriage. That's what pops out to people, without sort of all the other data.

So, you know, I just threw this out as well. This is the package insert for Tdap. You may or may not know there are two

vaccines that we really are trying to increase coverage rates in pregnant women, both. It's flu and then Tdap for their babies.

And, again, it's interesting, these are two different Tdaps, Tdap inserts. And, you know, again if you look at the one on the left, it says under nursing mothers, it's not known whether Adacel vaccine is excreted into human milk. Well, that's a great endorsement that, you know, gets people to start wondering. And then the same thing on nursing mothers.

So how do we give the information in a way that people, that physicians can digest it? Because when physicians see, I don't know, certainly with vaccines, we've had the experience if we know what that means.

So this is my last slide, which is basically if there is insufficient information on the label and/or there's no clear recommendation from either the ACIP or all of the professional societies, the assumption is that any given vaccine is unsafe to use in pregnancy or postpartum with breastfeeding. And so you get people who say exactly these words. I don't think so. Can't write it for you, can't prescribe it for you. Nope, not going to happen.

And so I think we have to recognize that when we're missing information, that is going to be very challenging, how to communicate that. Thank you.

DR. BLALOCK: Thank you for your presentation, Dr. Riley.

It looks like Dr. Berube has a clarifying question.

DR. RILEY: Yes.

DR. BERUBE: It's kind of weird, looking the other way.

I've done some work in nanomedicine, and we work in the area of some of these vaccines. I just wondered if you've considered -- I mean, the first thing to understand is that the public is distinctly different from patient, as a sample. There's a transition that takes place when somebody becomes a patient. There's other issues. And maternal disease syndrome is an example of that, right, where there's a unique relationship that takes place.

My question is have you looked at this Wakefield effect? Because we've been finding that when we do our research, that it just -- it's been bleeding into this vaccine world in dozens of different ways. And even when it's totally irrelevant, it doesn't matter; it's just bleeding into it.

Wakefield's the guy -- sorry, you know, who claimed autism was linked to --

DR. RILEY: MMR.

DR. BERUBE: -- some vaccines. And I think that's an important component that we have to look into. There's so many irrelevancies that just creep in, and we've got to figure out why this happens, more than that it's -- we know it's happening, but like why is it happening is the critical issue.

DR. RILEY: I agree with you. That's part of it. I think

also though, in terms of specifically to the label, when there isn't information, the assumption is, well, you know, Wakefield must be right, it must be autism or, you know, whatever the information is out there. I think that it's automatic to go with negativity.

MS. ROBOTTI: Hi. Just to bounce off what you said, as a layperson, I know that the flu shot is different every year. And I know that the studies were done on a flu shot that wasn't done this year. So you need to -- we as a -- you know, what needs to be made clear to a layperson is that the studies on the flu shot that happened several years ago are completely inapplicable to the flu shot that you're getting this year.

DR. BLALOCK: And that was Dr. Robotti.

Dr. Slovic.

DR. SLOVIC: Thank you. Paul Slovic.

Just very quick, to touch on your last points, which we could spend a lot of time discussing, and that is we've come to appreciate that our perception of risk and response to risk is dominated by our feelings, not by our analysis of statistics. And the language conveys feelings that can be very powerful.

In your last slide, you used the phrase "insufficient information." Now, that carries negativity. It's not a neutral term. Also, no recommendation is a negative term as well. So I think we have to consider very carefully the language which we, you know, logically we think is okay. How

is that going to communicate on the affective side?

And this is very testable. One can study this, see these negativities. Then you think, well, okay, now what do we do about this? Is there a more neutral frame that is still valid?

DR. BLALOCK: Okay. And I don't think I see any more questions, so thank you, Dr. Riley.

And our last presentation for this morning session is Dr. Elizabeth Conover.

MS. CONOVER: Can you hear me? Good morning. Thank you so much for inviting me to speak on this. It was sort of a little bit like you have 10 minutes to discuss how we did the Constitution of the United States, because it is a topic I am passionate about and I think is incredibly important.

So I am a teratogen information service person. I've been doing this for over 30 years and changed my mind many times about how I think is the most effective way to do this.

Today I am going to talk a little more about -- thank you. Today I am going to talk a little more about the perspective from then. I'm going to talk a little bit about how we think about conveying risk. And I will say, I am humbled by the Committee, many of whom I have read your articles and learned from. So we'll talk briefly about that, you know a lot about that, and then a little bit more about our efforts to convey risk.

Hopefully this goes forward. Maybe not. There we are.

My single disclaimer, that I receive information, as do another 11 teratogen information services, that comes through HRSA for support of educational research and service activities.

And so we've mentioned OTIS and MotherToBaby a couple of times today. Just to let you know a little bit about us, we are a completely nonprofit, as we say, nonprofit group of about 100 people who do clinical teratology. So we're interested in the applied part of all of this. And we get together to talk about our problems with lack of data, what do we do with conflicting data, how do we convey this information in a way that people can make decisions, in terms of doing it.

And so I would say that we do specialize in knowing where to find data, squeezing it out of lots of places, including the label, but then much more importantly, synthesizing it and highlighting the most relevant and important components. It's probably, besides conveying it effectively, the most difficult thing I do every day.

What do I do when there's no data? What do I do when there's too much data? What do I do when there's conflicting data? And really, nearly every day of my professional life, I've made decisions about how I'm going to handle that on a question about teratogen exposures.

I do think we work very hard at how you can have the best data in the world -- and let me say we do not generally have the best data in the world, but we have what's out there -- and

not be able to convey it to someone in a way that they can use it. And that's both the provider and the patient. It's extremely difficult.

And so I have a lot of sympathy, as we try to work on the label, for manufacturers and other people who are trying to put the information out there. It's a difficult situation.

And then I will say we, very early on in OTIS, we recognized that there was not sufficient data, and that if we wanted to have it, we were probably going to have to participate in gathering it so that we did have answers. We got really tired of saying, wow, that's a great question; it's really too bad we don't have information on that.

So I am going to go over, really quickly, just a couple of things because speakers before this have already done it. But I was part of Dr. Greene's original group in 1997 that came together to talk about what didn't we like about the pregnancy label. And so I think I did a little happy dance when they said they'd finally get rid of the A, B, C, D, X codes. We'd seen lots and lots of problems with them.

I will say getting rid of them has caused newer problems, but I do like the format. I do like the fact that they're helping us with more data, in both pregnancy and I'd like to see it in lactation too. And I like the expanded clinical considerations.

I will say this is one of my -- whack-a-mole is one of my

favorite analogies. But the providers and pharmacists are really unhappy about getting rid of the A, B, C, D, X codes. And they haven't been super reassured when I've said, oh, you'll love the narratives, in terms of doing that.

And so they say, that's nice, Beth. And I'll say they're really not very accurate, and they aren't updated, and all of these things. And they'll say, that's nice, Beth. And they still use them. Or I'll go through and I'll explain all of this data, and the physician on the hotline will say, okay, can I use it or not, or what's the code? And I'll say, no, no, no, no, no, we don't do that. And they'll say, oh, just whisper it.

(Laughter.)

MS. CONOVER: Just tell me what that code is, in terms of doing that. And so, like most teratogen providers, I started out overemphasizing risk, hazards, harm because, well, honestly, no one is probably going to sue you for emphasizing harm. The medicolegal aspects of it are there.

I've always wanted to be fair to a patient. I think -- or a provider. I think they do need to know if we suspect there are harms. Those do need to be balanced against the risks. And so, again, it's easy to start with that. It's easy to go on and on and on about the harms. But I now start every conversation I have, whether it's with a provider -- and that's primarily I answer questions from providers -- or a patient

with discussing the situation that the -- the indication and the benefits.

I make it my business to talk about the benefits because it's so easy to not do that. And speakers before, like Dr. Wisner, have talked about that. But it needs to be balanced. You can scare anybody with the information or lack of information.

And so I do think, also, let me say that we need to say what we mean and mean what we say. And that means occasionally going out on a small limb, hopefully not a big limb, and say what we mean.

And so I did want to remind you that most providers probably don't go directly to the label. They get it from something like Lexicomp, or many providers like UpToDate. And so, again, I pulled this one off a couple of weeks ago. And you will notice there is that pregnancy risk factor still up there. They keep telling them they need to get rid of it. But the pregnancy risk factor is giving some information in a very succinct fashion.

Now, I could argue forever that, you know, condensing trimester and dose and reason for use and alternative medications into that code, you know, is a terrible idea and -- but when you have 32 seconds to try to decide, and you're balancing it against, you know, will this work for what I need to use it for, does it have side effects, will it interact with

the other medications or whatever, they want a way to start to very simply get some idea of what they're dealing with.

I will say this current UpToDate one actually had something on the physiologic changes and the pharmacokinetics. And I was happy to see that, in terms of doing -- this happened to be one on escitalopram.

I also want to say something about the codes, which is that providers frequently use them to compare drugs in the same category or even among categories. And I have struggled, personally, when they call me. I do that comparison for them. I'll say, well, here's your choices: this, this, and this. What are you thinking will work the best? Let's talk about the fetal risk after you've thought about what you want to use.

But this happens to be a patient handout, but it's -- these kind of things are done all the time in professional articles, where you're using it as kind of like a quick thing to compare. And so when you're thinking about what you really want to use, codes have been kind of useful. So what do we put in their place? And I'm still struggling with that.

Here's my favorite cartoon forever on this topic. And I'm not saying that patients are dogs, by the way, just that I think it's a great example. "Okay, Ginger. I've had it. Stay out of the garbage. Understand, Ginger? Stay out. Stay out." And what they actually hear, "Blah, blah, blah, Ginger, blah, blah, blah, Ginger, blah, blah."

And my patients will say, because I am a talker, as soon as you said the word "congenital malformation," which I don't use birth defect, as soon as you said something that I heard, my anxiety went up, I didn't hear the rest of what you said. You've got to get it in fast, in the first couple of sentences. It's so easy to information dump with providers or patients. And, you know, I might feel better. Boy, did I just give a really comprehensive discussion of that; hoo, am I smart. But did they understand what I said?

I do want to mention a couple of people that had a big impact on me, by the way, including all of you, of course. Gideon Koren, who was at Motherisk and now is in Israel actually, was one of the first people to start looking at the fact that women really overestimate risk. Their perception, their pregnancies are so dear to them that it's such a threatening situation that the responsibility of being pregnant, that they tend to overestimate risk. It's also some of his data, again, suggests that providers overestimate risk, in terms of doing it. I will say, Janine Polifka, who edits and writes TERIS, and I'll show you our databases at the end, was a long-suffering co-author on the article we wrote on teratogen risk communication, and John Paling, who I thought did some interesting early stuff on conveying risk.

So we've talked about a lot of these. I already mentioned pregnant women and providers tend to have kind of distorted

perceptions of risk. It's really a problem that our data is limited and contradictory. And it's just true all the time. And I worry constantly about things we don't know, like things about behavioral and neurocognitive kinds of things. We really, really, really don't have sufficient data. And those are really important.

You know, we can fix a cleft lip and palate pretty easily. Intellectual disability, much more difficult, in terms of doing it. And I do find, over and over again, that this is true for providers and patients; no data either means big risk or no risk, not much in between.

Again, risk is contextual. It doesn't matter what the risk is for. And I again note that risk is more acceptable if it provides them with benefits, as it should be, and it certainly is individualized.

All right, so uncertainty, and I deal with uncertainty every day. It is again one of the more difficult things. I think all of us -- they say if we thought about every decision we make, with all of the ramifications constantly, you know, we would not step out the door. We probably wouldn't get out of bed.

But what we're talking about is uncertainty. We actually cannot prove risk or prove safety, but people prefer black and white situations. That's how you make easy decisions. And so the problem is this is all uncertain. And the spectrum of

risk, every time I try to explain that to a patient that, no, this is not yes/no, this is a spectrum of risk, it's uncomfortable, and it's hard. I don't want to give them information in a way that they can't make a decision.

And so, again, patients and providers tend to cope with uncertainty by either saying, oh, so you said there's no risk? And I think, oh, I don't think I ever would have said that. Or she said there was a risk, and so I didn't do it. I mean, just absolute. And I do think that's one of the reasons the FDA codes are appealing is there is a certain black and white aspect to it. The nuance is all gone, but people find them easier for that reason.

And so most of you are already interested in health literacy. I will say that most of what we're talking about is conveyed numerically, but it is a really difficult area for people to handle. And some of the data on physicians, highly educated people are that they don't handle certain aspects of numeracy.

I want to mention framing because I think framing is something we all do. Sometimes we think about the fact that we're doing it, and sometimes we don't. But one of the things I noticed in the label, of course, is that we're always talking about the risk of having an adverse effect rather than the chance of having it not happen.

And so as any good teratogen counselor, I always flip it,

no matter who I'm speaking to. If I'm saying, I think there might be about a 2% risk of cleft, 98% of the time it won't happen. I do it every time. And I don't know how that, how easily that fits into the label. I will say, conspicuously, they're only talking about loss.

And already we've talked about a couple of cases where relative risk makes the risk look huge. You can really scare people; you can scare providers and patients by using relative risk. It's helpful in research, but it isn't very effective in conveying things to patients or providers in a way they can use.

And so when we can, we try to actually use absolute risk, and so again, the excess of the risk over the baseline population. And many times we're talking about a rare malformation. We've increased the risk, but it's still very rare.

One of the things that I found when I started doing the -- and you've heard me use the word "risk." It's impossible for me to get rid of that term out of my vocabulary. I will say, as a genetic counselor, I make it my business to speak about chance, chance and probability. I am trying not to attach the negative.

And thank you for bringing that up, by the way, Dr. Slovic, because I think we do it all the time. And so, anyway, in OTIS, we work really hard on getting the word "risk"

out of our fact sheets when what we really mean is chance or probability. We usually use the term "chance."

And then one other thing I want to remind you of, and I again see it all the time, is when you're using fractions, people tend to rely on the numerator and ignore the denominator. And we ask people to do hard things. Again, I find this even true to be with healthcare providers, that you're asking them to compare across different denominators, and people cannot make very good decisions. So the question is would you do something like that within your label where you're trying to keep your denominator the same across various studies? Maybe.

So after I got kind of spooked on numbers and realized -- and patients tell me, well, that number didn't mean anything to me. Thanks for sharing that with me. I do think we need to use numbers. It shows you know what you're talking about. Patients and providers deserve numbers. But since people have a hard time with numeracy, I got into using verbal expressions of likelihood, low risk, high risk.

I had this whole little vocabulary of it, and I thought I was really just doing a fabulous job with that. And then I read some of the data on the fact that, for example, there was a study that the word "likely" included anything from 0.5 to 0.99 chance of happening. Oh dear.

And then I love the word "low risk," or the two words "low

risk." And, again, there were people that considered low risk to be like 10% to 25%. So, obviously, I was not conveying what I had hoped to do. I haven't given up on these verbal expressions, but I use them more carefully, to be honest. Okay.

So to go through and talk a little bit then on what kinds of things we've tried to do, again, I've talked about the trying to keep the denominator the same and using -- with patients, all the time I say, you know, if there were -- if I saw 100 women, 3 of them would have a baby with a birth defect. I try to put it into natural terms. I go out of my way to avoid decimals, in terms of doing that, and I go out of my way to avoid relative risk, especially when I'm talking about a very rare event.

I'm using verbal expressions of probability more carefully, in terms of doing it, but again, there is data that you can combine it with a numerical risk and use it as a way of -- I must say, I think most people, providers and patients, get the idea of what I'm talking about by my tone of voice and my facial expressions if they're sitting in front of me, so I need to control that more probably.

And then, again, I really -- as I say, I'm very careful about framing probability by showing both sides of it, the hazard and the -- but also the chance of having a healthy outcome too. I really do think it's terribly important.

Again, I do use the word "chance." I try to do that, and I do provide numbers in different formats. And I do find patients, some patients really, and providers like percentages; some don't. Some do better with ratios or whatever. And so I will phrase the same thing in several different ways, trying to catch what's going to work for that particular person.

As almost all genetic counselors, we love visual aids. And so I've tried lots of different ones. The one that you see up there where they're showing all the people in the auditorium and that -- one of the problems with pictograms is that you can actually, again, do it in a way that it sometimes will cause overestimation of probability that -- and the same thing can be done with nearly any graph.

You can make, by how you design it, you can make it look really hazardous or really reassuring. So it needs to be done carefully, because again, we want to be balanced. We want them to know some of the hazards. We want them to know that it doesn't always -- nothing happens all the time and that we're again comparing this to their benefits. And so trying to be balanced about this has to be the most difficult part of all of it. All right.

So this is one of the things we actually -- well, exactly, there's one more part to it, thank you -- that we designed for a recent little article we wrote on treating depression in pregnancy. And, again, well, there's that "medication risk"

word again there. But we are talking about hazards there, in terms of doing it. And I'm not saying that this is anything perfect. And even when you have a hazard, you might still use medication.

So what we're kind of just trying to suggest again is a spectrum of the way someone might weigh it. I don't think this is perfect either, but I do think sort of visual things like this might help a provider as they're trying to -- I talk a lot of family practitioners through -- they've prescribed an antidepressant. They're starting to worry about it; the patient is pregnant. Again, what are your hazards, what are your benefits?

And then one of the things I stumbled across, maybe you guys all know about it, was that there's a plain language thing that's coming out of Health and Human Services. It's been there for quite some time, but I found it when I was getting ready for this talk.

One of the things I liked is they suggest organizing information so the most important action points come first. I try to remember to do that. It's easy to bury it under, you know. So you really need to do that. I am a big fan of bullet points. I haven't seen the labels done that way. Maybe that would be too colloquial, but people that are reading them tell me that they can't concentrate all the way through them, even though they're incredibly smart people. So these are

providers, say oh my gosh.

Simple language: I personally think even providers need language that is simple. I noticed in some of the labels, by the way, there's a lot of acronyms. And patients definitely do not know what acronyms mean. And providers tell me they have to stop and think about what it is. So sometimes you're not saving space to do it.

Lots of white space, if you can: Again, maybe consider graphics or visuals. We've have to think about how that would go, maybe just in terms of what the background risk is for birth defects, for example. You might do that, in terms of doing that.

I did want to show you and end with a couple of examples of what other people in teratology have done to try to do this. And they would tell you this is imperfect. So here is -- we use a couple of different databases, several, and TERIS is one of them. And they have gone to this, there again, trying to use verbal, where they talk about both the magnitude of risk and the quality and quantity of data, and then comments, in terms of doing that.

So they -- and they'll tell you what each one of their words means, in terms of how they're using -- they are consistent about it. But unfortunately, or fortunately, the words they use aren't always the same as what everybody else would use in interpreting that risk.

Let's see. Here's REPROTOX, and they, after I don't know, maybe 10, 12 years ago, went to putting out one- or two-sentence Quick Take. So it's interesting again. And providers tell me, sometimes that's all they get to. They'll take a quick look at that first couple of sentences.

Then if you want to look at it, you can see all of the animal data, human data, and it goes on and on and on, all of the references underneath it, in terms of -- I have to say, I look at the Quick Take first. Then I go through and read it because it's my job to know what I need -- you know, everything. But for a provider who's got a couple of minutes, it's an interesting way to do it.

Here's LactMed, which again has gone to using a couple of sentences at the beginning to summarize use. So, again, busy providers take a look at the first couple of sentences, and then if they have questions about it, I know they don't go on to read the whole thing unless they have a situation they're uncomfortable with or that again the patient asks them for more data or whatever.

And our MotherToBaby fact sheets, which I have to write some -- and I will say, I teach a class in teratology, a graduate course, and I know that what my students think is going to be the easiest part of the course; I have them do a research project on the teratogenicity of a particular agent and also use in breastfeeding.

And then I say, okay, convert that into a patient fact sheet, and I'm suggesting you get started early so that you can come and talk to me about it once you start doing it, because it's very difficult. It's very difficult to write in a balanced fashion. All of my students start out way -- they information dump, and they way overstate the hazards.

And as we try, I say so do you think the patient could actually make a decision based on that? And they say no. So, I mean, we move through the process of trying to convey that, using words that people can understand. We have chosen to break it up by a question-answer kind of a format.

Patients used to our fact sheets and even providers that go in and read know that we're going to go through, you know, what is it, does it affect fertility or cause miscarriage, does it cause birth defects, does it cause neurobehavioral things, and breastfeeding, and then that we are always, towards the beginning, talking about the benefits. What are the benefits? This is how you need to be thinking about it.

So we have about 150 of these. I always -- they're free. They're in Spanish and English. I always recommend them. I think that they're a nice way to back up when you're speaking with a patient or a provider, that information.

But we still struggle. We struggle with when to update. How much information are we going to put in it? What studies are we going to cite? What do we do when there isn't data? So

we're going through the same things as people do with the labels. It's painful.

But we do it because you know what? Doing it is better than not doing it. It being painful and hard is no excuse, because out there are women who need to take these medications every day and providers who need to make decisions about this. It's not going to go away. You can't put your head in the sand. They're out there, they need the information, they need it now, and they need it in a way that they can make a decision.

And that is the end of my -- that's the beautiful Nebraska skyline. Thank you for inviting me.

DR. BLALOCK: Thank you, Ms. Conover. And I actually have a clarifying question as well. You know, in your presentation, you know, you mentioned, you referred to various formats for presenting risk information, absolute risk, relative risk, you know, etc., using the verbal, you know, verbal descriptors. And the FDA may need to chime in on this.

My question is that in the rule as well as in the guidance documents, I didn't see any requirements for how the information needed to be formatted, with respect to that. So my question is, are there any aspects of the rule that do specify the format for the information?

DR. YAO: So the requirement is to incorporate the information that we have in the framework that we're given.

The rule really talks more about how to format content rather than, per se, absolute requirements for content. And there are some areas in which content is required, so if you have the information, you are required to include it. If you don't have information, for example, then you are required to include statements that say that. But as it relates to risk, absolute versus relative, no.

DR. BLALOCK: That's what I thought.

Let's see, Dr. Nahum. And, again, you know, please, you know, clarifying questions.

DR. NAHUM: Yes. Dr. Nahum.

You know, it seems to me, from you've said, that there are really three different types of categories to be considered: One, the first one is conditions for which a pregnant woman was previously on a medication prior to pregnancy for which she should continue to be treated for something. Second is a new condition that arises in pregnancy. It's not pregnancy-specific. And that would be something like a UTI or asthma or something like that that arose during pregnancy. And then the third one is something you didn't talk about a lot, I don't think, which was pregnancy-specific conditions, which are things like preeclampsia, preterm labor, etc.

And I guess my question is I wonder if you could distinguish a little bit amongst those three different categories, because I think that in the case of preexisting

conditions, OB/GYNs often do medication adjustments or changes or whatever in conjunction with other physicians who prescribe medicines prior to the pregnancy.

But the other two conditions of things that arise during pregnancy could either be in consultation with other physicians or just by an OB physician. And, clearly, the pregnancy-specific conditions are mostly just by OB physicians. So could you talk a little bit about these different sort of categories and how you view them?

MS. CONOVER: Wow. I will say the majority of the questions I get are either from a OB -- OBs use our practice, our teratogen service a lot -- or the previous specialist. The patient's had the condition, had them on a medication that didn't take into account whether or not -- that was not necessarily one they would have planned the patient to be pregnant on.

And so the decision is now that you know they're pregnant, is this still the best medication? Usually we're not thinking about do they need to be treated. We're needing to think about is there something else that might be lower risk to the fetus that will provide adequate treatment, and we all agree the patient still -- they have ulcerative colitis or something, in terms of doing it.

And I will say, you know, that women take a lot of medications for a lot of things. And there is that weeding out

thing. There are some things where they say, well, you know, you might want to use that cream for your wrinkles when you're not pregnant, but let's talk about maybe not doing that when you're pregnant. You can go for a while without it.

So there is sort of that -- the obstetricians have that kind of issue that comes up during their first couple of -- first prenatal visit where they're looking at what was prescribed by someone else, making sure that's where they want to go, usually minimizing the treatment regime in the sense that they kind of try to consolidate what really needs to be treated, what doesn't, and then are we using the right thing? I answer a lot of those questions.

I answer a fair number of something new comes up during pregnancy. Again, usually they're considering, do I need to treat this? Obstetricians are careful people. And they know that they have a big medicolegal thing, and they're careful about it. And so I find that they aren't asking me anything wild usually, in terms of doing it.

Sometimes it's new providers are -- I teach in the medical school, and so it's talking about that thought process and getting kind of your own little cache of drugs you know a lot about and feel comfortable with in pregnant and breastfeeding women.

I don't get as many calls about things like preeclampsia and stuff. It may be those are often third trimester things.

We get asked about gestational diabetes sometimes. But a lot of those things, obstetricians have kind -- they deal with it a lot. They've worked it out. There's kind of a company line on those. I don't answer those as often.

I'm not sure I answered your question, but my familiarity with those situations has to do with, they don't need to ask me for something they already know. And so there's a lot of discussion about some things. I am dealing with more their uncommon stuff that comes up because patients have a lot of different problems.

And so -- oh, we have a transplant program. I'm often called in on people that develop cancer during pregnancy. I often talk again about the benefits of treatment. It's easy to avoid treatment, and we've had patients die during pregnancy or die right after delivery from cancer when the treatment would not have been -- it would have had risk to it but not nearly the risk of the death, in terms of doing it.

So I think I'd love to talk to you about -- I bet you have great thoughts on this.

DR. BLALOCK: Thank you.

MS. CONOVER: Thank you.

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: Hi. I had a question concerning providing numbers.

You said that you work to avoid decimals. And I was

wondering if there was any data, sort of, about what works most effectively for ratios versus fractions versus percentages, because I know, for example, in university classes I've taught, and granted, these are social science majors, so their numeracy can be really high or not so high, that they didn't know what fractions translated into in terms of ratios or percentages.

And I didn't realize this until I said, so how many people would that be in this classroom, and everyone looked at me sort of dumbfounded. And so I was wondering is there any, other than us just sort of having these impressions, is there data that exist that suggest what works best for people?

MS. CONOVER: And I can see people nodding. There are people on this Committee that know more than I do about this. But I will say, in talking to patients and providers, sometimes one format works better than the other. That's why I was saying that I will frequently provide it in several different ways. You try not to confuse people by doing that, but to put it into perspective, in terms of doing that.

So the decimal thing's kind of easy. Even providers don't handle decimals all that well, in comparing them. But I do find, in talking to patients, that some patients prefer percentages.

Even when I'm talking about the risk for birth defects, I will say, 3% background risk, 3 out of 100. I'll put it into -- you know, if 100 women walked into my room, 3 of them

would -- I mean, I am -- or conversely, 97% of them would have a baby that did not have a -- I mean, so you are tossing around numbers, but you can just see it clicks with some people.

And I'm often talking to a couple, in person, and you can see sometimes that the man, something will hit him, that he'll handle say percentages better, and the woman might like the natural number better or whatever.

So, and again, I'll see an optimist or a pessimist in couples. And it is another reason, besides just the framing thing, to be showing it in 97% chance of a healthy outcome versus 3% chance of a birth defect. So it's really personalized.

In fact, one of the things I thought about in this presentation is I have -- except when I'm writing the evil fact sheets, I am normally personalizing my information. I already know and have asked where are they in their pregnancy, why are they taking this, what -- you know, how much do they really need something?

I have lots and lots of information. The label has to work as a generalized kind of piece of information, whereas I know that I can highlight certain parts because that's what's relevant to this case.

I have to be careful that I don't bias it tremendously by that, but that -- so I'm personalizing it. That might be the easy part of it. Doing it in a generalized way that works for

a lot of people is hard.

DR. BLALOCK: Okay. And I'm pretty sure that we're going to be discussing that a lot more tomorrow.

MS. CONOVER: Yes. I bet you will.

DR. BLALOCK: Just in the interest of being able to get to lunch, one more question, and that's from Dr. Lyerly.

DR. LYERLY: So thank you for the talk.

I was -- I really appreciate your attention to language and particularly to the use of the word "risk." Obviously, that comes up with particular intensity given that you're a teratogen information service. And the word "teratogen" has an etymology to it too, that raises a lot of concerns.

But I was wondering, you know, in your efforts to sort of mitigate the fear -- and I don't know, this might be not a good way to go, but to mitigate the fear associated with drugs, remind people that there are other kinds of teratogens besides drugs, maternal disease being one of them, right, so metabolic diseases, infectious diseases are also teratogens in themselves.

And there's a way in which kind of softening the language of risk could be one approach, but there's also a way in which helping people understand that drugs can be teratogens, but diseases can be teratogens as well, might have an effect on the ways that people understand sort of the range considerations.

MS. CONOVER: Thank you for clarifying that for me. But

it's the other reason that I always compare it back to the background risk when we're talking about malformations or background risk for miscarriage, if we're taking about miscarriage, or background risk for intellectual disability, because that not only -- you have to be careful about mentioning 10 things that can go wrong in pregnancy because pregnant women are nervous about it, unless they're just exceptionally placid people.

It's a time of anxiety. And I mean, not that it wouldn't be lovely to be placid, but you know, it's a time of anxiety. We can easily stir that up, and they don't hear what we're saying. I mean -- and I know I don't. You know, mention the word "cancer" in the first sentence, and I might not either hear the next three paragraphs.

So we're careful about how we do that. I would never want to -- I don't use the word "safe," to be honest. I use "reasonable choices"; I use my own phrases like that. I really would never want to pull the wool over the eyes of a provider or patient in doing that. I do think everything is contextual, and everything is comparative.

And my favorite comparison is that, you know, in a perfect world, with no exposures at all, you still have a 3% chance that your baby might have a birth defect. And for a lot of women, they've never heard that. Some women have said, well, why did I call you if you're just going to make me nervous

about my 3% background risk?

So, I mean, you know, we're not all things to all people. But I do think that's important for them to know that. And I will frequently say, well, you already started out with a 3% background risk, and this added, you know, half of a percent to it. So your risk went from 3% to 3½%. Think about what that means to you and in the context of how important this treatment is to you.

So I am always backing into that. And I'm so happy that the new labels do give a background risk. Many women tell me they are not aware that they have a background risk for adverse effects, that everything must be causal, must be due to what the doctor prescribed or something they did wrong.

DR. BLALOCK: Thank you very much.

So we're at the lunch break. I still need to remind Committee members not to speak about the topic of the meeting, either among other Committee members or with members of the audience. And that's just so that we can have all the wisdom here and on the record.

We'll resume exactly at 12:45. And so I ask everyone to come back on time. And then Open Public -- people who are speaking at the Open Public part of the meeting after the break, please see Lee.

Oh, some other very important things. There's a room in 1504, that's left out of the room, for members to eat. And

guest speakers, 1408. So guest speakers, 1408, to the right. Members, 1504 to the left.

That's it. So I'll see you at 12:45. Thank you.

(Whereupon, at 11:50 a.m., a lunch recess was taken.)

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

(12:49 p.m.)

DR. BLALOCK: And I'd like to resume the Committee meeting. We'll proceed to the Open Pubic Hearing portion of the meeting. Public attendees are given an opportunity to address the Committee, to present data, information, or views relevant to the meeting agenda.

Lee Zwanziger will now read the Open Public Hearing disclosure process statement.

DR. ZWANZIGER: Thank you, Dr. Blalock.

Welcome to the Open Public Hearing. Please state your name, your affiliation if relevant to this meeting. Also if you have any financial interest relevant to this meeting, such as a company's or group's payment of your travel or other expenses, FDA encourages you to state that interest as you begin. If you do not have any such interests, you may wish to state that for the record. If you prefer not to address financial interests, you can still give your comments. Welcome.

DR. BLALOCK: For the record, there's one written comment received in the public docket. The docket remains open for additional comments for another month.

For today's public hearing, we've received one request to speak, and the speaker has 5 minutes. We ask that you speak clearly to allow an accurate transcription of the proceedings

of the meeting. Dr. Shapiro.

DR. SHAPIRO: Thank you for the opportunity to speak today. I am Dr. Danielle Shapiro. I am a physician and senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers.

Those are the perspectives I bring with me today. We do not accept funding from the pharmaceutical industry, and therefore, I have no conflicts of interest.

Based on the discussion questions, we have the following comments: Number one, what factors are meaningful to interpretation of risk messages? Well, a Dutch study published in 2017 found that 35% of pregnant women were concerned about birth defects and 35% about miscarriage. The majority of women responding to the survey, however, took medications during pregnancy, with acetaminophen being the most common.

Women were most likely to perceive harm for antidepressants, sedatives, anxiolytics, and NSAIDs. Women were most likely to believe benefits outweighed the harms for antibiotics, antifungals, and antacids. Importantly, the study identified pregnancy trimester, parity, marital status, smoking status, and family history as important factors in women's interpretation of treatment and risk benefits.

Number two, how effective are the communications provided

in the product labeling under PLLR to date? While we don't yet know how effective it has been in increasing provider knowledge or changing clinical practice, based on FDA's 2009 mental model study of 54 providers, drug labels are not the providers' first source of information.

Perhaps that is because the old lettering system was too simple and did not provide sufficient or useful information. The study demonstrated that provider confidence and treatment decisions increase when quality data on human use were available. However, when those data are not available, interpreting or extrapolating data from animal models is likely to increase confusion. Based on the mental model study, providers want simple yet clear information in order to meaningfully and effectively communicate treatment risks and benefits to patient.

Number three, what are the best practice approaches to effectively communicate risk in a manner that is helpful to prescribers and pregnant women?

Well, there are many approaches to effectively communicate risk in a manner that helps rather than hurts decision making: (1) Frame risk as positive versus negative; (2) Emphasize beneficial outcomes of treating a condition in a pregnant or lactating woman versus the probability of harmful outcomes, which are likely to be quite low; (3) Communicate risk in absolute rather than relative terms; and (4) Use visual aids

such as icon arrays. The 100 face Cates Plot is a great example.

So in a survey of pregnant women with urinary tract infections, actually just 30% reported not taking these treatments. To help women make informed decisions, we need to emphasize that while the chances of a common antibiotic causing an adverse fetal effect are probably less than 1%, the absolute risk of preterm birth and low birth weight in women with untreated UTIs are 16% and 12% respectively.

Unfortunately, studies show that patients and providers alike have difficulty with numeracy, especially around understanding and communicating risk. This makes it difficult for patients and their healthcare providers to make informed decisions about treatment.

Using icon arrays to demonstrate both baseline risk and incremental risk increases could help to illustrate numerical concepts, which will enable patients and providers to reach well-informed treatment decisions. In addition, approaches that create essential information resource are likely to be effective.

The question-answer service that's offered, actually, in Norway, called the Regional Medicines and Pharmacovigilance Centres, or RELIS database, serves as a really good example. A study of 45 providers who used the service found that it increased provider confidence and reframed their risk

perceptions.

Likely, a free, independent-run information service in the U.S. will help patients and providers to individualize treatment decisions and balance the risks and benefits for patients and their families.

Thank you for the opportunity to share our perspective today.

DR. BLALOCK: We've got one clarifying question for Dr. Shapiro.

Dr. Robotti.

DR. SHAPIRO: Yes.

MS. ROBOTTI: Hi. I don't know if you have this information on hand, but you made a comment: Drug labels are not the providers' first choice of information. Maybe everyone else knows the answer, but what is their first choice?

DR. SHAPIRO: Sure. So this mental model study was almost done 10 years ago, but likely those practices are similar today. I can say that as a prescriber myself, I mean, you would look at things like UpToDate, point-of-care resources such as Medscape or DynaMed. I don't want to name-drop or anything like that, but definitely the label is not the most well suited for point-of-care quick information. But we could change that. Thank you.

DR. BLALOCK: Thank you.

Does anyone else in the audience wish to address the

Committee at this time? Members of the audience. And if so, you know, you can come up to the podium and state your name.

(No response.)

DR. BLALOCK: And I don't see any additional comments. So let me ask the Committee, we only had one speaker for the Open Public Hearing. Does anyone else have any clarifying questions for Dr. Shapiro?

(No response.)

DR. BLALOCK: It looks like we don't, so I will pronounce today's Open Public Hearing to be officially closed, and we'll proceed with today's agenda.

So the next speaker to start out the afternoon session is Ms. -- and I may butcher this name -- Zahlaway Belsito.

MS. ZAHLAWAY BELSITO: Thank you very much.

I am technologically challenged, so I apologize in advance. Waiting for my slide deck to come up here.

I don't have a disclaimer slide on my patient perspective slide deck here, but I do want to state to the Committee and to the open forum that I do work as a consultant with SAGE Therapeutics in regards to a drug that's still in the Phase III for postpartum depression, and I have been remunerated for such.

So I have been asked and was graciously asked and received the invitation here to give a patient perspective to the PLLR Task Force. And I did label this "Pregnancy and Lactation

Labeling Role - A Modern Day X Factor." The X factor definition is a variable in a given situation that could have the most significant impact on the outcome. And to me, this outcome is the health and wellness of the mom.

So what is a mother-to-be to do? I'm going to give you a little bit of a brief personal perspective here, as I was a mom who was not quite sure as to what options were or were not available when it came time to utilize an SSRI. So I'll be speaking on my specific perspective on that.

The lack of information, consistent information at that time, to the public, i.e., me, regarding safety around medication and pregnancy, I believe, prohibited me to make an informed decision about taking medication, and this also due to over-the-counter medications as well.

I felt that social stigmas around the health and wellness of the baby -- I think Dr. Wisner alluded to that, how we're all supposed to just be beaming joys of light during this time, with nothing but a sleeping child that is exhibited on the Pampers box when you go to buy it. When I find that baby, I'm going to hold it, because it never cries.

So the social stigmas around the health of the mom versus the health of the baby, it's always how's the baby doing? The focus is always on the baby, and it's never on the health and wellness of the mom. And this, I believe, creates this potential added internal conflict dialogue to the mom to say,

I'm supposed to do everything and be the sacrificial lamb, so to speak, in a lot of this.

I always joke around; I say the word "ma" is actually short for martyr, because you're supposed to just be completely giving of yourself and no longer focus on your own health and wellness. So, again, the mom should not put her baby at risk -- oh, it says "risky"; my apologies on the typo here -- risk by taking medication with no known outcome during pregnancy or not a clear outcome. And mom should put her own health and wellness at risk, again with the martyr factor, due to no known outcome of taking medication while pregnant.

And my own personal decision going on my second pregnancy, because I did suffer from mental health, OCD, anxiety issues with my first, was to completely wean myself off, which in retrospect wasn't that much of a very kind process to the body.

So to take or not to take the medication, that is the question, okay, from the mom's perspective here. And what I did -- and I'd like to say thank you to folks who reached out and worked with me -- I did a crowdsourcing on moms who were pregnant and had been pregnant in the January 2015 to present-day time period, to speak specifically to the regulations that were -- at least the recommendations released out of the FDA on medication and its usability during pregnancy.

So, "PCP had me on an old-school med that was safe for

pregnancy because she knew I was trying to get pregnant." And the old-school med, again, my apologies, I have here was for blood pressure, okay, blood pressure. "Once I started fertility treatments, the MFM specialist suggested a better med that I'm now on, and the PCP went along with that recommendation."

"I am early on in my first trimester, and I feel terrible physically, but more concerning is my anxiety and depression and how I feel mentally right now. I am no longer taking any of my anxiety medications because the doctor told me to stop months ago, to prepare for getting pregnant." This individual is currently in their first trimester right now.

Continued, "I told my OB/GYN I had wanted to get pregnant in 2015. OB/GYN told me I would need to come off of all my medication before trying to get pregnant. I was on Prozac, trazodone, and a very low dose of Xanax. I stayed on the first two until the fall of 2016. I was working with a reproductive endocrinologist at that time, and I decided to wean myself off in the fall of 2016 before I became pregnant. I've been off all meds since then. I delivered my baby girl in 2017."

The second bullet point, "I was advised to stay on my psych medication when I got pregnant in 2016."

"Currently pregnant and told by my psychiatrist and a high-risk doctor to stay on my meds, on Luvox 200 mgs once daily, Abilify mg once daily, and Adderall 30 mgs once daily to

counteract negative side effects."

I want to put out here, and I had worked with Dr. Cathy Spong on this one -- I had the honor to speak at the PRGLAC Task Force as well -- that what we see with moms is what I term, and others term, doctor shopping. Who's going to work with me to take my meds? And sometimes you'll see even just a disparity, city versus country.

I can go to Boston and get someone maybe at Mass General Hospital to work with me there. If I go up the North Shore to a smaller hospital, they're going to be less inclined to work with me. So whom do I end up going to see at the end of the day? I'm going to end up going to Mass General. And I don't think that that's consistent messaging in how we're taking care of the health and wellness of moms.

"I was advised to stop taking Celexa before I got pregnant."

"I was on 50 mgs of Prozac and was told to go off. My nurse practitioner weaned me off in less than a week. I was a hot mess."

"I was told to stop my Lexapro by my OB/GYN."

Now, again, I want to point out again, these are all folks that have been pregnant from January 2015 till now and have had successful pregnancies with no complications. I do also want to put that out to the Committee here, that there were no issues with the child that was born.

"I was almost 12 weeks when I started Lexapro. My OB/GYN was completely on board, knowing what the alternative was to not being on anything." So, again, one way this way, one way the other way, no consistency in the application.

"I found out I was pregnant with twins. OB told me to stop my psych meds, and I went to a prescriber to wean me because I was scared of just stopping." From that story right there, they did wean her. They didn't opt to suggest that she stay on.

"Pregnant in 2016-2017. Stayed on Lexapro. My OB and my perinatologist were all totally fine with it. Baby had an echo done, and my perinatologist, when I was in my second trimester, added as a precaution. Everything was and is fine."

"I had a doctor wean me completely off my psych meds when we were trying to conceive. He did it really fast. It was absolutely awful, and I ended up in the hospital."

"When I became pregnant in 2015, I was back on a very low dose of meds and with a different doctor. He slowly weaned me off of that, and it was fine. He wanted me to go back on the meds toward the end of my pregnancy, but I refused." And this was 2016.

So as you can see with these snippets here, everyone has their own story, who they worked with, what provider, what choices they made, what medication they were on, and these are preliminary on psych meds that I speak to. I'm sorry. I

completely jumped over my skis here in the beginning.

I am a Commissioner on the Postpartum Commission, the Ellen Story Commission with the Commonwealth of Massachusetts. I am a maternal mental health expert in the field. I do work with federal and state legislatures on policy, all surrounding the health and wellness and moms and their mental health.

I did -- my apologies for not putting it out there. And I am the founder of what's called Effie's Grace, which is a small advocacy firm that advocates for positive policy outcomes in women's healthcare and wellness. So I speak to this issue from that of a patient, and then that as an advocate, with moms going through this every single day. And I think it's incredibly important to be aware of the inconsistencies from the mom perspective.

So our observations, collectively, as moms who were taken off psych meds and self -- there are moms who are taken off psych meds and self-medicate themselves into addiction. I think we've all been hearing an incredible amount of substance abuse issues as of lately. When we take a look at a state like West Virginia, I believe it's 40% plus of their births right now are all addicted to substance abuse.

And we're seeing the same thing in Massachusetts, seeing relatively the same thing in every single state in the United States right now. And even when it comes to alcoholism, we were having some lunchtime conversation over folks being taken

off of their psych meds and then utilizing alternative substances that aren't monitored and the adverse outcomes of what that looks like, right.

So we want to ask the medical community, that if there is clear and consistent guidelines and a helping hand, like Beth from Nebraska, and you folks that are tasked with working with the moms, it's going to alleviate, I think, a lot of negative outcomes of self-prescribing and self-medicating that we are seeing.

The doctor-shopping piece, I put in there again. One doctor will monitor the pregnant mom on meds; another will tell the pregnant mom no meds. And so the lack of consistency there is incredibly confusing, especially one pregnancy to another.

I am going to go off the cuff here by saying that there are some folks in the autoimmune disorder arena who have shared with me, there are patient advocates that have shared with me, first pregnancy, they took no medication for a form of fibromyalgia, and it was a horribly painful birth that was excruciating for them, etc., etc. They had a beautiful baby.

And then 2 years after, when they were pregnant again, they found a doctor who was willing to work with them and keep them on a medicine regimen, and they had a very successful, very lovely pregnancy. And so the outcomes -- I don't think she's gone for a third. But the outcomes of those two pregnancies were night and day.

The need for provider training to utilize existing PLLR information and support evidence-based care is crucial. We need to take -- the collective we need to take into account both risk of illness and the medication treatment.

Some recommendations here are to create an online tool that hosts all agency info related on medication safety, a database for pregnant and lactating moms. Now, I know, you know, it's like you've got your college kid who's going to self-diagnose on WebMD, right. That's not exactly who I'm talking about here.

It's also why we say don't keep trying to self-diagnose yourself on the internet because it generally leads you into you're that one person in the world that has whatever this odd illness is.

But we're looking for informed, consistent information that moms can take a look at. Maybe if I go to see my OB and they say X, Y, and Z to me, I'm able to go back that night to my own home or on my phone, because everyone has this digital interaction now, and will be able to read the same exact information that was given to me that day, right, not a disparity of information but consistent, clear information, and allow that mom to make the decision and come back and say, you know what? I read about it; I thought about it. We had more than 5 minutes in your doctor's office. Now I'm prepared to make that decision.

And I think giving people the power to make decisions for themselves, especially where you're becoming a new mom, is very important to make the patient feel empowered in making those decisions that are, again, based on clear information.

OBs should have access to consistent data regarding medication and pregnancy. Info should include caveats that the data -- and another typo here, my apologies -- that the data available is the best data available. And I know we were talking about how that information continues to circle. And I'll let the experts in that space be the ones to answer how best as to do that, how best as to update, keep the updated information coming. And decisions need to be based on the health and wellness of the mother-to-be.

Again, I want to stress how much the focus is always on a successful and healthy birth, to potentially the detriment of the mom. So I always go back to the airplane attendant who says in case of an emergency where we lose our oxygen, you put the oxygen mask on you first before you put it on any other members of the family that need help or children. And that truly is it.

Unfortunately, when it comes to maternal mental illness -- and Dr. Wisner spoke to this briefly earlier -- some folks that end up in a suicidal ideation or in a psychotic episode, the worst-case scenario with these folks when they're taken off their medication is that they either -- that either a suicide

occurs and the mother is no longer here, and then there's nobody to take care of the baby incidentally when that issue occurs, or there's a horrible situation where there is filicide and homicide, and we can save those stories for later. But there are incredibly extreme consequential outcomes when it comes to mental health and psychomeds, so --

Again, this is my contact information. I've been very honored to speak here in front of this Committee. I was very honored to speak in front of the PRGLAC Committee as well. And I also want to say I do have an incredible amount of tentacles, so to speak, into the moms across social media and within a lot of different states and avenues. So if there are any questions that can be posed to me, I'm more than happy to connect you with whomever that population is that you're looking to speak with.

So thank you very much. If there are any questions, I'm more than happy to answer.

DR. BLALOCK: Thank you very much.

Do any of the Committee members have brief clarifying questions?

Dr. Joniak-Grant.

DR. JONIAK-GRANT: Hi. With the findings that you were looking at, did you find any differences for people -- for example, if their main symptoms were pain, you gave the example of the fibromyalgia case. Was it seen more as that's not so

much about health and wellness as about just, from the mother's perspective, sort of getting through it because it's pain, and at the end you'll be done? Were there -- versus kind of saying like, oh, well, this is a mental illness that could get worse, or this is, you know, a diagnosis I have that could get worse. How did pain play into sort of their expectations?

MS. ZAHLAWAY BELSITO: I appreciate you asking that. I can say that being in the Cambridge Boston area, there's a lot of patient advocates that are working on a lot of different autoimmune issues, etc., etc. So I spoke to a lot of colleagues in the space that work with patient ambassadors and then the moms themselves.

And to be honest with you, no, it didn't matter. It was don't take medication. You are pregnant. Don't take anything, including acetaminophen, including ibuprofen. And so when we get into the OTC, there's a lot of -- I feel really bad. There's a lot of people out there with acid reflux, okay. But that wasn't applicable to this Committee.

But my point with that is, is that, you know, people, they're being advised to stay on the Zantac, you know, stay on whatever that preventive medication is, over the counter. And then it starts to become a lot more blurry when it gets into the actual prescription space. So there was no differential. It was don't take the medication, whatever the issue is, because ultimately it's the health and wellness of the baby

that you're putting at risk. And that was the -- again, the message, the focus is on the outcome of the baby and not the mom.

DR. BLALOCK: Dr. Tracy.

DR. TRACY: Thank you.

I was just wondering what your experiences were, and perhaps how these women handled these various issues, whether they were a first-time mother, or maybe this was their second, third, or fourth pregnancy, with regard to sort of how they managed with their caregivers, how they kind of managed maybe with their partners or spouses, and how all that kind of played out.

MS. ZAHLAWAY BELSITO: Thank you for the question.

And, again, I can only speak to anecdotal stories, evidence, etc., that I've heard. I could give you a whole gamut of experiences, and I think that there are some folks that I'll use, again, the maternal mental health challenges experience that, say, their third pregnancy, and there were no issues prior to the prior two. And then they subsequently went on to have two more.

Well, if they didn't find the likes of a specialized mom-baby unit or specialized health practitioner, such as Dr. Wisner or Samantha Meltzer-Brody at UNC, etc., to actually go through therapy and set up a plan to address this issue the next time around, as far as support systems go, people are kind

of just flying by the seat of their pants on this. And even the OB/GYN in that circumstance doesn't have much recommendations to bring to the table.

Again, it could be specific practices that do. I think we see in New York State, by mandate of Government Cuomo, they're doing a lot more in the space. But, again, you know, am I going to get better service in New York City than I am going to get in Rochester? I don't know.

But the majority of moms I spoke to -- again, with the mental illness, this is an issue that people don't want to necessarily talk about or aren't as transparent. And I think we're going to see changes in the generational.

I think you see a lot of millennials will be the first to be like, oh my gosh, that bipolar medicine I was taking, that one just wasn't working. You know, and you were like, wait, you were just not supposed to tell anyone that you're having mental health issues. You're supposed to keep that inside.

And I'm saying that jokingly, not because I think that we're going to see a generational change with the way that we address a lot of stigmas that we're dealing with in society, that there's going to be more transparency on the patient end of things than there will be necessarily, that's going to -- than there are as present day that's going to drive a lot of this conversation to change.

Where I think, when it comes to pain management or

ulcerative colitis, etc., etc., those aren't things that are shameful, per se, because they're a physical ailment, right? So there's a known physical component to that, where you have anxiety or bipolar or other issues, it's more of a, you know, I'm not -- maybe I shouldn't even be having children because maybe I'm not fit to be a mom. So then there's a lot to unpack with that as well.

But I do think that if there was more guidelines on how to access support systems, or how to manage this from a family unit and community support systems, that that could also be helpful. But there's not -- it's not baked in there as it is right now.

DR. BLALOCK: Dr. Goldman.

DR. GOLDMAN: Myla Goldman.

Thank you so much for your presentation. I had -- I'm having a hard time sort of synthesizing a single question. I think there's so many launching points from what you presented.

But I guess what I'm wondering is based on your experience and what you've, you know, come across in the study that you did is the difference between women living with chronic medical conditions versus specifically outside of the realm of affective disorder or depression, where the effect of the disease itself is maybe better characterized or better understood, so thinking about asthma that was brought up.

The disease that I deal with, which is multiple sclerosis,

where, you know -- and you have specialists that are engaged in that conversation -- I'm just wondering if these are sort of two different populations that we need to be thinking about communicating with. Or do you have a sense of like the more doctors at the table, the better it is or the worse it is or --

I'm just -- a lot of the examples were differences between, you know, what the patient wanted or the doctor said, or differences among patients, which each got a clear message but the message was different, as opposed to the OB and the neurologist or the gastroenterologist and the family practitioner, you know, those types of mixed messaging. Can you comment on that?

MS. ZAHLAWAY BELSITO: I again can only comment on what I myself have been involved in and what I've heard through boots-on-the-ground, grassroots folks. You just made me start to think about another way to approach this, and that is just based on evidence-based treatments.

If I look back to my experience in 2013, and then all of a sudden in 2014, in the Commonwealth of Massachusetts, there is a psychiatry access project for moms, so that any healthcare provider can actually pick up a phone and get a real live psychiatrist to consult with. Now you have a team. You now have a team that's communicating based on -- and it's not just the individualized OB and the patient, right.

You were just talking about that. That's like coordinated

care. You've got the neurologist with the OB, or the XYZ practitioner with the OB. And then you bring in the maternal fetal medicine specialist into that, if it's high risk or IVF. But when it's just me, myself, and my Lexapro, right, then there is no -- that's my only team. And so that there doesn't engage another source to bounce.

So going back to the example I gave in the Commonwealth of Massachusetts, my experience would have been much different if there was access to a maternal mental health psych that could have done coordinated care with my OB. And I think that that's an advantage that we should look to see how do we best equip OBs in this space to address the number one complication of all pregnancy, which is maternal mental health complications.

I mean, that is the reality of it. It is the number one complication of all pregnancies is adverse mental health challenges that are temporary and treatable. But if you don't treat them, they will manifest, unfortunately.

DR. BLALOCK: Dr. Lyerly.

DR. LYERLY: Thank you for that presentation.

I was wondering if you had any sense of how women think about their decisions to take or not take medications in the longer term. So they either decided to take the antidepressant or they decided not to take it based on inadequate evidence base or however the risks and benefits were communicated to them.

So how does that sort of decision-making process affect their thinking about their own health or their child's health into the future? Did you get any sense of that from your boots on the ground?

MS. ZAHLAWAY BELSITO: I did. And so I submitted some additional comments, I believe, that are in the back of our package here. It's fairly lengthy. It has to do with the fact that I think I need glasses, so I made sure that this font was rather large. But these pages here in the back are also covering the lactation period, okay.

So that's as far as I can -- I can speak about my own engagement on that. I was very successful at breastfeeding my child. When I finally hit a wall with the OCD and I went to look to speak to a psych about it, the recommendation was the Lamictal, of which was that gradation at the time, a C. And it was recommended for me to completely stop breastfeeding and get on that, to take care of myself.

Now, the consequences, the adverse consequences of not breastfeeding would have been, to me, really been kind of the straw that broke the camel's back, right. So it was, you know, kind of a dead end here and kind of a dead end here. Now, once there was additional conversation past that one medication, and kind of past the management of being a fully capable mom, there were different discussions to be had.

I'm speaking to the breastfeeding piece, which I know is

part and parcel of this task force, but necessarily of this discussion, that again, the lack of consistent data on that point, on the postpartum piece, is as credibly difficult to navigate as it is with the pregnancy, because of the safety precautions around it. Yes, you can take an SSRI. No, you can't take the Lamictal. You shouldn't be on the lithium. Okay, try to take the Prozac. Well, that's not working, try Celexa.

And so it ends up becoming like a Russian roulette of what's going to work. And even if none of them work, well, those are the only ones that we think that you can take so, you know, then stop breastfeeding.

And, again, the stigma piece around this I think for moms and medications are don't take the medication. You know, be a martyr. Make sure that your vessel is holy clean and that you are doing everything in the best interest of your child, because if you're going to pollute it -- you know, we're not talking about a glass of chardonnay at 5. You know, we're talking about whether or not you're going to stay on your medication so that you're okay.

But, ultimately, is that going to cloud over into my breast milk? Is that going to cloud into my ability of being a mom? And so I think that there is a lot of strands that roll out of this overall conversation.

But there are some moms who sent me a note, adamantly, I'm

so glad I went off of my antidepressants. It was the best thing I ever did. I still am having mental health issues, but it's okay because I stopped taking the medication. And so there's that like self-flagellation part of it as well that is kind of a difficult situation to address.

So I apologize if I didn't answer it succinctly to what you're saying, but I think that there's, again, a lot to unpack with this overarching dialogue as it relates to the medicine and the mom.

DR. BLALOCK: Thank you very much.

MS. ZAHLAWAY BELSITO: Thank you.

DR. BLALOCK: Our next speaker is Dr. Spector-Bagdady.

MS. SPECTOR-BAGDADY: Hi. Thank you for having me today. My name is Kayte Spector-Bagdady. I'm faculty in the Department of Obstetrics and Gynecology at the University of Michigan Medical School.

So I'm going to talk about three main topics today: first, the varied stakeholder interests that are at play in the case before you -- and I think the staff did an excellent job of bringing forward representatives from all those different stakeholders to talk with you; some of the legal constructs that are at play, both the labeling regulations but also sort of liability and malpractice considerations; and then some of the complicating factors that the intersection of these create.

And lawyers like to start with the good news, and I would

say that the good news is that this is so complicated, it'll make for a really good teaching case, but other than that, I'm not sure.

So first to talk a little bit about the stakeholder interests. First, of course, we have primarily the pregnant and lactating patients, and ultimately we're here for their best health and welfare interests, and as we've heard, their potential increased physiological risks of taking medication while pregnant and lactating, but also, very importantly, as Dr. Wisner walked us through, the risks of foregoing medically necessary medication during pregnancy or lactation, which are sometimes just as important as the risks of taking them.

And then also of primary concern to both the clinician and the pregnant or lactating women is the health and welfare of the fetus or the baby. And often, in clinical care, we're tasked with ensuring that we weigh the risks and the benefits to the patient in front of us adequately, but it gets that much more complicated when the risks and the benefits might be different for the woman or her fetus or baby.

Next, we of course have the clinician's interests. And as we know, she has a duty of care, both legally and professionally, to her patient to prescribe medications and dosages as she deems fit within the applicable standard of care as well as part of her practice of medicine.

But she needs adequate information to do so, presented to

her in the most effective manner possible. And as we heard in overview, when FDA convened their focus groups in 1999, they found that clinicians wanted as much information as possible, and also got feedback that the previous system of A, B, C, D, X where 60% of our products were lumped into Category C weren't adequate to do that.

And then regulators -- government workers are people too. I'm a former fed. Regulators have their own interests, right. And as Dr. Yao went over for us, FDA, we believe in the mission. They're here to ensure the safety, efficacy, and security of human drugs.

And we've already talked a little bit about the importance of the rallying cry of the thalidomide disaster to this. But this has really led to very profound safety and efficacy evaluations, once again, to help and protect the patient.

And the drug developers and manufacturers and marketers also bring to the table their own interests. Most of them are for-profit entities, but they're there to develop and market safe and effective products that clinicians will prescribe.

And then, of course, all of these parties have interests between them, the regulators and the regulated market. Drug developers and manufacturers have direct relationships with clinicians either through advertising, detailing, marketing, and then regulators and clinicians also have their own relationships. So this can get very complex.

And then, of course, we have our legal constructs. And I'll go into this a little bit more deeply because that's what you flew a lawyer here to do. But essentially, some of the main ones are, of course, medical malpractice claims between the patient and her clinician, which hopefully are rectified or absolved through the informed consent process.

There are sometimes direct product liability claims from the patient against drug manufacturers and developers, which they hope will be somewhat rectified by the learned intermediary doctrine, which I'll talk a little bit more about. And then, of course, we have labeling regulations, whereas feds, the FDA regulates the industry to ultimately assist the doctor in doing that informed consent practice.

So to talk a little bit more about products liability, so drug and device cases are a huge portion of our federal case load. And as Professor Conover also talked about, we know that 15% to 20% of pregnancies already end in miscarriage, and up to 3% of pregnancies are affected by birth defects.

And so in order to have a tort law claim, you have to have a duty, breach, causation, and an injury. We know that doctors have a duty of care towards their patients, and this is a really large potential injury base that we don't necessarily know what caused those injuries. We don't necessarily know what happened, why the person miscarried, why there's a birth defect. But that is a large pool of potential litigants. And

as Professor Conover said, all risk must be causal is something that many patients subscribe to.

And then we have the learned intermediary doctrine. So whereas in general products liability, manufacturers have a duty to warn the end user of a product, for prescription drugs, the clinician herself acts as a learned intermediary between the manufacturer and the patient, such that generally a manufacturer's duty to warn is fulfilled by warning the clinician, who then has a tailored conversation with the patient.

So as a quick example, I think it was just mentioned and not gone that much into, is a case study of Bendectin, which was authorized by the FDA in the 1950s for nausea and vomiting caused by pregnancy and was used across the world for almost 30 years and in over 33 million pregnant women.

But the first case alleging a birth defect from Bendectin was filed in the U.S. in 1977, and the FDA convened a panel to review the scientific literature and actually found no association between the drug and birth defects. But in 1983, Merrell Dow decided to pull the drug off the U.S. market because there wasn't enough of a profit margin between selling the drug and their litigation and insurance costs.

And some subsequent research even found that when Bendectin was pulled from the market, hospitalizations for these pregnant women for nausea and vomiting increased rapidly.

So, then again, that's an example of sort of a failure of a cost-benefit analysis.

And then we have medical malpractice claims. And whereas general clinicians believe their risk of being sued is much higher than it already is, OB/GYNs are right; they get sued a lot. And a recent ACOG survey found that 74% of OB/GYNs have a professional liability claim filed against them during their career, and that's an average of almost three claims per clinician in their lifetime. And almost half of these clinicians reported making a change to their practice in response to these specific liability concerns.

And we also know that doctors are supposed to act within the standard of care, again, duty, breach, causation, injury. And so we talked about the duty, we talked about the injury. But a breach of that duty is usually going to be measured against the standard of care.

So the law doesn't generally prospectively prescribe a specific standard of care. And it's actually based on evidence of customary practice or what a reasonable practitioner would do in a similar situation. But it's important to note that that standard of care is not necessarily synonymous with best or evidence-based medicine.

So it's not evidence of effectiveness, but evidence of practice. And clinicians in the past have been found liable for violating a standard of care that's not actually supported

by the best or most recent data.

And so I actually had a recent article that came out with my colleagues at the University of Michigan -- Ray De Vries, Lisa Harris, and Lisa Kane Low -- that there are situations in which practitioners actually who are concerned about liability implications stay away from -- they're sort of risk averse to the standard of care. But if all clinicians are acting in ways that are risk averse to the standard of care, that can actually serve to shift the standard of care.

So then they're getting -- you know, judged against these risk-averse actions as opposed to what it should be, which we described as the standard of care sprawl. And we used the example of electronic fetal monitoring when we were doing that because there is many, if not most, circumstances in which electronic fetal monitoring is actually not prescribed. But you can see where this might also be very applicable to implications for prescribing drugs for pregnant and lactating patients.

And then we have informed consent. And sort of the classic iteration of what informed consent means is it requires capacity, information, and freedom from coercion, but we're here to focus on the information component. And, you know, it's important to note that just because we get informed consent doesn't necessarily mean the clinician doesn't have to meet the standard of care. They do. And just because you're

acting within the standard of care doesn't mean you don't have to get informed consent. You need both.

And what we're trying to balance in this informed consent discussion is both the autonomy of the patient -- so patients must not only give consent, they must give consent that is informed -- but also it must be tempered by the clinician's ethical duty of beneficence.

So, for example, clinicians are supposed to take into consideration the patient's mental and emotional condition, their level of education, their own values and priorities. And this is something that only the clinician can balance herself with the patient sitting in front of her, because clinicians and patients obviously come to the table with completely unequal information. And that's why the patient's there in the first place.

And there is this real tension between autonomy and beneficence that needs to be tailored. We need to give the patient enough information to enable a knowledge decision, but not so much that the patient is confused or overwhelmed. And this fine art of disclosure balance plays a large role in this last area, which is the labeling regulations.

So as the Supreme Court has summarized this in the past, ultimately the manufacturer bears responsibility for the content of its label at all times. Quote, "It is charged both with crafting an adequate label and with ensuring that its

warnings remain adequate as long as the drug is on the market."

And this intersects with the standard of care in sometimes interesting and sometimes confounding ways. So the majority of jurisdictions in the U.S. accept drug labeling as evidence in support of the standard of care, in addition to expert testimony. So it's not the sole determinant of what the standard of care is, but it can provide significant assistance in establishing it. And only a few jurisdictions actually have held that labeling is, on its face, the standard of care.

The American Medical Association recently came out with its own position statement, which reads, quote, "Official labeling should not be regarded as a sole standard of acceptable or accepted medical practice, nor as a substitute for clinical judgment or experience, nor as a limitation on the usage of the drug in medical practice."

But just like informed consent between the clinician and the patient, again, these drug labels are about disclosure balance. And in 2006 FDA wrote, somewhat optimistically it turns out, that labeling should establish both a floor and a ceiling of disclosure.

Quote, "Given the comprehensiveness of FDA regulation, additional requirements for the disclosure risk are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate

judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug."

And then in 2009, that other branch of government, the court system, said check on the executive one. And in this famous case, a Vermont musician went to a clinic for a treatment of migraine and received an IV push of the anti-nauseal Phenergan rather than an IV drip. Phenergan entered the musician's artery. She developed gangrene, and unfortunately, her entire forearm had to be amputated.

So Wyeth labeling had warned against intra-arterial injection and said it was preferable to administer its drug via IV drip, but it did not specifically warn against IV push. And Wyeth argued that the fact that FDA had approved its labeling, so that if this federal agency had approved its labeling, would preempt any state tort law claims.

And, generally, manufacturers may only change a drug label after FDA approval, but there is a change in being effective regulation that allows drug manufacturers to do so in a case of additional risk or contraindications.

And, therefore, the court found that because there is this exception, there was an avenue for manufacturers to update the label even before FDA had approved it, and therefore, it was not impossible to comply with both federal and state and that the FDA labeling regulations did not preempt it, which means that even though FDA might say that is the appropriate label,

there might be state tort law claims that might still be levied against clinicians for prescribing according to that label.

So as you can see, there are lots of different stakeholder interests that might or might not fully align with all of the legal mechanisms that we've set up to protect them. But so, ultimately, I'm going to clear away some of this noise and focus on what we're really here about, and what we're really here about is this informed consent discussion.

And in order to have a really clear conversation about informed consent, I think we need to introduce another stakeholder, which is data tracking and research. And it's that data tracking and research that's ultimately going to generate the kinds of peer-reviewed publications that we need to inform both clinicians directly, as well as the drug manufacturers, such that FDA can require, then, that they disclose back to the clinician such that she can have the best informed consent discussion possible to the pregnant and lactating woman.

And, of course, these are regulated by yet another regulatory regime, and I hate to even say it out loud before July, but those are the human subjects research regulations.

So I'm a research ethicist at heart, and so I must have a slide on the research ethics of this. And certainly want to acknowledge all of the important groundbreaking work that has come before me on this, particularly Drs. Annie Lyerly, Maggie

Little, and Ruth Faden, and their Second Wave Initiative; the Office of Research in Women's Health; the Task Force on Research Specific to Pregnant Women and Lactating Women; and some of the IOM Committees, who have found time and time again a sort of unnecessary exclusion of pregnant women from research and many IRBs considering pregnancy, on its face, a cause for exclusion.

And we really need to continue to include pregnant and lactating women in this research, not only to help future women and their babies like them but also because, quite frankly, some of this research has potential benefits to these women, and they're being excluded from being involved in them, because quite frankly, if we're not conducting research with pregnant and lactating women, we're just experimenting on them all.

And the typical approach of postmarket drug surveillance is quite biased. We know. We've talked about this. Dr. Sahin went into this for us. But, you know, if we only report adverse events when clinicians or patients bother to do so, they're much more likely to be major, and they don't give us the necessary prevalence data against which to weigh them.

And so what we really need to be doing is gathering this data over all facets, again, guidance and encouragement of pregnancy exposure registries, many of which are run by the manufacturers themselves, clinical data registries by professional organizations such as ACOG, retrospective cohort

studies.

But all of these are still ultimately just data silos, right. You have to go to all of these different registries; you have to pull all this different information. We've heard about busy clinicians not necessarily having time to amalgamate all of this information themselves. So we really need to continue to encourage broad data generation sharing and use.

So, moving forward, this is my last slide. What does this mean for us? So we are here today to talk about disclosure standards. And hopefully I've given some helpful information about relevant legal constructs and liability towards that. And, certainly, we have the right people around the room, the preeminent experts on communication of risks and health benefits here already.

But ultimately here, the outcome of interest to us is the improved health of the pregnant and lactating women and their babies. And this theme that we've heard throughout the day is that this is actually ultimately an information problem to which the disclosure issue is actually secondary.

So I was the Associate Director for President Obama's Bioethics Commission for 6 years, which is also a federal advisory committee. But I'm not a fed anymore. I'm an academic, so I get to say stuff like this. But just like we have data silos in clinical care, in research we have health policy silos in the federal government, right.

And so we have an NIH, an FDA, and OHRP, and the Office of the Secretary, and they really are all working towards the same overarching goals -- I believe that, they believe that -- but not necessarily in the most consistent ways possible.

And so, yes, methods and order and type of disclosure is critical. And we should focus on that, and we should work towards the things that we have power to achieve. I acknowledge that. But just as critical is having the best information to disclose.

And so I would encourage you, in your deliberations, to also not lose the forest for the trees and ensure that labeling regulations and your communication recommendations enable and align with best practice methods, such as observational data gathering and research incentives, to make sure we're disclosing the most helpful information possible in the best ways possible.

Thank you.

DR. BLALOCK: Thank you very much.

Dr. Nahum, you have a brief clarifying question?

DR. NAHUM: Yes, I do.

You know, just looking at Slide 5, I have a question, because I think you said something perhaps that you didn't mean to say. And I'm reading the top bullet point, which says drug and device cases, these comprise almost 45% of the federal case load.

I want to refer back to the FD&C Act, as amended, and the preemption clause that exists there for medical devices. This is broad. It's in force. And it has pretty much limited medical malpractice liability vis-à-vis product liability for manufacturers as that CDRH approval of medical devices with appropriate labeling, with appropriate manufacturer packaging, labeling, distribution effectively exempts all manufacturers from tort liability for those products.

Now, if you meant to say combination products, then I understand this, in the case of the drug device combination or biologic device combination or another combination which does involve a medical device. But in and of itself, I do not believe that medical devices would comprise any substantial portion of this 45%.

MS. SPECTOR-BAGDADY: Yeah. I think that that's really fair. It's a good clarification that certainly prescription drugs and medical devices are regulated differently because of this explicit as opposed to implicit preemption in the medical device amendments. I don't have specific data. The researchers who put out the 45% didn't break down the drugs versus devices versus OTC, but I'm happy to look more into that and send you it. But I don't have that on hand.

DR. BLALOCK: Any other brief clarifying questions?

Dr. Baur.

DR. BAUR: Cynthia Baur.

So my question has to do with your model for stakeholders. And I'm curious why you left out politicians, since they provide the policy framework. And I'm thinking, if in our deliberations we come to the conclusion that maybe it's a combination of information and policy, I'm just wondering how your framework would accommodate that.

MS. SPECTOR-BAGDADY: Yeah. I like that observation. I guess when I was thinking of stakeholders, I didn't think of -- perhaps erroneously -- politicians as bringing their own personal interests to this table that was somehow different than that of the best interests of patients and clinicians and the U.S. health system.

But, certainly, Congress has a lot of power to act in this space, particularly as we were just discussing in the area of express preemption. So I don't think that that would be wrong to add them as a stakeholder, but that was my thinking as sort of when we're really boiling down to the lobbying and the interests and the advocacy, who we're working towards, it's really these entities.

DR. BAUR: Well, I think, particularly in light of our previous speakers' observations about really the politics around motherhood, that I would definitely encourage you to think about politicians having their own spot in your map because I don't think that -- as a mother, I don't know that politicians' interests always align with mine.

MS. SPECTOR-BAGDADY: I would agree with you. I think that's a fair addendum.

DR. BLALOCK: Dr. Nahum.

DR. NAHUM: Thank you. I do have one more clarifying point here.

Towards the end of your talk, I think you were alluding to the fact that real-world data of various sorts, especially with approved drugs and biologics, would be useful to collate, process, and ultimately analyze to be able to come up with better paradigms with regard to benefit-risk ratios in various settings for different types of drugs and biologic products.

I guess I have a comment and a question about that. When we collect real-world data, even when these drugs are approved, as far as confounders are concerned, there are those that are known, there are those that are unknown, and then there are unknown unknowns. It may be potentially possible in large databases that are consolidated to control for some of these in some cases.

But in the case of biases, and I mean here, prescriber biases, access biases, patient selection biases, etc., these cannot be controlled. They cannot be expunged, and they cannot be eliminated. And this will result in all cases in biased findings, biased results, and will cause people, patients, practitioners, institutions, and governments to believe, in many cases, what is simply not true.

So how do you reconcile this with the last several slides that you presented, advocating for the use of this type of poorly or uncontrolled data to better inform us as to what to do?

MS. SPECTOR-BAGDADY: Well, so one possible solution to poorly and uncontrolled data is power. And that's why we so often don't find out about adverse side effects to drugs and devices until they go onto the market. And instead of having hundreds of people enrolled in our clinical trial, suddenly we have hundreds or tens of thousands of people who are actually taking the drug.

And I acknowledge that certainly there does not exist an ideal solution for this at the time, which is why I closed with the argument that whereas we don't have the ideal solution yet, what I would encourage us to do as we work towards it is at least not work in ways that undermine the ideal solution, and that we need to keep into consideration, as we make all of these smaller decisions, how exactly to order this, how to disclose this, what should we do in X, Y, Z cases, that the ultimate goal is this kind of data generation and data building that will help us all.

And I think that the more data sharing and the more data use we can do, the better that will become. But I agree that we are very far from the ideal solution at this point.

DR. BLALOCK: And one final clarifying question,

Dr. Cappella.

DR. CAPPELLA: Joe Cappella. I just wanted to check on something that I think I heard you say, or that I may have misinterpreted, and that was the comparison between standard of care and labeling information, and that in some senses, that just because there was an accepted labeling information for a pertinent drug, that may or may not be the standard of care. So the standard of care may be to ignore the labeling or to put it in a subsidiary position. Is that correct, as far as you're -- as I understood you to be saying?

MS. SPECTOR-BAGDADY: So different jurisdictions have gone different ways, because ultimately this is a state law question. But the majority of jurisdictions have found that labeling, in addition to expert opinion saying that yes, this labeling is in fact what most practitioners follow in this situation, is generally accepted as a standard of care.

And there are only a few jurisdictions which don't require that additional expert testimony that testifies that yes, the labeling is in fact the standard of care, and they just accept the label on its face. So it's a bit diverse across the states.

DR. CAPPELLA: So what that might mean is that that in some jurisdictions, that the labeling might not be a motivation to the prescriber because it isn't necessarily the standard of care.

MS. SPECTOR-BAGDADY: Yes, that's correct. And, in fact, that's one of the concerns that I was trying to talk about, whereas if people are acting sort of in overly risk-averse ways, even though the labeling might say it's okay to do this in this situation, if everyone in a practice area in a geographic region is actually working in more risk-averse ways, above and beyond that which the label states, that could be the standard of care that the court finds.

DR. BLALOCK: Yeah. Dr. Nguyen, did you have a comment that you wanted to make?

DR. NGUYEN: Thank you. I actually have a question.

Thank you for that excellent presentation. You had mentioned that, I think it was 60, 70% of OB/GYNs have been --

MS. SPECTOR-BAGDADY: Yeah, 74%.

DR. NGUYEN: -- served a notice of lawsuit. And about half of them changed their practice afterwards. Could you clarify on what those changes were?

MS. SPECTOR-BAGDADY: Yeah. So that was sort of an amalgamated percentage that included a lot of different things. The ones off hand that I can tell you about are, for example, ordering tests that the clinician didn't necessarily feel were medically necessary but the patient requested them. And the clinician felt under some duty to order that just because they were worried that the patient was going to get upset or that something might happen and they might be sued.

The example that we were particularly interested in, in our article, was use of electronic fetal monitoring. We're working on that, whether clinicians sort of independently believed that that was evidence-based and appropriate in that situation or whether they did it because they were worried that they going to get sued.

And so mostly it involved the use of emerging technologies that the clinician didn't feel like necessarily was indicated but wanted to do in prevention of a lawsuit.

DR. BLALOCK: And one more question. Dr. Spong.

DR. SPONG: Thank you so much. Cathy Spong.

I'm going to follow up again on the standard of care and labeling, just because this is really circling for me to try to understand. If the labeling isn't specific to pregnancy but is specific for use in an adult, or an adult woman and she happens to be pregnant, is that enough for the standard of care?

MS. SPECTOR-BAGDADY: Well, so this is all up to juries, right. So what I say actually doesn't matter at all.

So, again, if the label is about the use of this drug in an adult population, and there's no information that's specifically relevant to pregnant women, the jury would probably be even more likely to look at evidence of practice rather than the label itself.

If the label were more specific and gave more information, I think that this is what some of the clinician focus groups

were concerned about back in 1999, was that the more sort of clinically directive information that's included in that label, they were concerned that the higher the possibility was that they would be sued for -- or not sued, because you can always be sued, but they would be held liable for not following what that exact label was.

So it's that constant tension in disclosure, that risk-benefit analysis not only vis-à-vis the patient but vis-à-vis the court system, vis-à-vis the jury, vis-à-vis Congress, vis-à-vis those that are regulated. So that's why it's so complicated.

DR. SPONG: Thank you. And is that risk of liability increased for both the provider and industry, the manufacturer, or separate?

MS. SPECTOR-BAGDADY: I'm sorry. So you're asking if the risk --

DR. SPONG: The information on the label. If you have more information on the label --

MS. SPECTOR-BAGDADY: Right. So that increases the risk potentially for the clinician more so than the drug manufacturer, because if you think of entities working in risk-averse ways, in sort of ways to prevent litigation, drug manufacturers are incentivized to disclose as much risk as possible such that they can say our duty to warn the clinician has been fulfilled. Then the clinician acts as the learned

intermediary who's supposed to adequately balance those risks and benefits for the individual patient sitting in front of her.

So I think that, ultimately, this is a problem for us all, but it's a litigation problem mostly for the clinician.

DR. BLALOCK: Thank you very, very much.

And we'll now move on to our final speaker, Dr. Traci Lee.

DR. LEE: Thank you.

Good afternoon. When I saw on the agenda that I was at the end of such an esteemed guest speaker list, it was a little unnerving. But I hope to give you some insights on the industry perspective, and we'll see how it goes.

Okay. So I've been -- so I'm a pharmacist by training. I've been working in the industry for 20 years. I've been working in labeling for about 12 years. And the reason I got the job in labeling was actually the PLR, Physician Labeling Rule, being announced in 2006. So thank you, FDA, for giving me an opportunity to go work in labeling.

The other thing, I hope -- this is just one industry perspective. I work in -- I've only worked in one company. It's one woman's opinion. So we'll just go through kind of my experiences on this.

Another thing I would like to say is I was talking to my 7-year-old that I was doing a talk on labeling. He's like, mom, that sounds really boring. I think you need to try to

make them laugh. So this is my attempt to try to make you laugh a little bit.

I will also say that I have a professional relationship with GSK. I get financial holdings and my compensation as part of my employment.

So as I mentioned, I wanted to give you one sponsor's view on the regulation, how we approach the regulation in terms of standardizing a process, the timelines, how we looked at the data evaluation to make sure we were pulling the right risk information in, also look at challenges, feedback we receive from FDA, and also insights.

I'm not going to touch on this because we've talked about the limitations of the categories in the earlier talks today.

Just in terms of the new regulation, when it was announced, we initially gave feedback in 2008 on the draft rule. And when we saw notification of the final rule in December 2014, we were quite excited to have this framework, to have these improvements in the labeling sections, to communicate risks and benefits more effectively.

We really appreciated the fact that you had the synthesis of data in the summary format, and also that it touched on untreated disease states, which was not there before, and also 8.3, the addition of that section.

So it was quite overwhelming. We were excited but quite overwhelmed by the amount of work that we needed to undertake

to execute this. What played into that was our extensive product portfolio, so we started planning immediately.

So I was one of the labeling point persons assigned to this from the beginning. And to start this, we had to consider not only new products being written to meet PLLR but also look at all of our established labels. And because GSK had proactively converted a lot of our labels voluntarily into PLR ahead of the regulation timelines, we had very few older labels, and we knew that all of those PLR labels would require a lot of work. So we started as soon as we could.

We created a cross-functional small PLLR sub-team that had core members on it: labeling such as myself, a physician from safety, Ph.D. from epidemiology, expert from non-clinical and clinical pharmacology.

We met several times to define an internal process of who would do what, who would contribute to what sections. We made sure that management was in agreement with our proposal. We had to gain safety board governance approval on our plan.

And then at that point, we went about creating briefing materials, which included slide packs, broad email awareness that we could send to all those disciplines within the company. And then we would always -- the identified sub-team would be the points of contact should anyone else in the company have a question related to their discipline.

So I'm not going to go into too much detail on our

internal process here, but I just wanted to point out, on the left column -- sorry. On the left column, these disciplines, it was clear that each functional expert had an accountability that aligned to what was expected to meet the regulation, in terms of that section of the label.

So those folks went on an individual team. They were assigned. They went away, did kind of their searching, their review of the data, their evaluation, and kind of brought their pieces together to the larger team, where we then looked at the data presented in its totality.

And one other thing I wanted to point out on this slide is prior to PLLR, we already had an internal safety panel, called the Pregnancy Outcomes Advisory Panel, that's made up of non-clinical and clinical experts, OB/GYNs, epidemiologists.

DR. BLALOCK: -- to speak louder.

DR. LEE: So this panel was already in existence. So we took the opportunity, with all of these label updates, to take the revisions, whether they be new labels or converted labels, to this panel for input. So this was just kind of another level of review that aided consistency. It allowed us to see broad kind of differences across therapy areas and see what we can learn from those different therapy areas.

I won't touch on -- sorry. I keep moving away. I won't touch on this slide either, because we've talked about the timelines over the 3 years, but what I will point out is I

mentioned we have a broad portfolio with more than 80 labels. And when we looked at the timings for the June 2018, '19, and '20, you can see the buckets of how our products fell.

That was going to be a lot of products' labels to get revised in those, kind of the weeks or months leading up to those time points. So what we had to do was change that, and I'll talk about it on the next slide.

I also want to reiterate again that because most of our labels were in PLR format, we expected significant changes to occur. They would be submitted as prior approval supplements, a lot of discussion with FDA. We had less than five that were not in PLR format that would only require removing the category.

And then just to mention one thing in terms of Dr. Greene's comment earlier about Lamictal, so we have Lamictal, and it's in this middle category, is due June 2019 based on its last approval efficacy supplement. But like I said, we're trying to do them earlier, and Lamictal is actively being worked on now. So while I don't disagree that the labeling currently needs updating, we are actively working on it as a sponsor.

So in terms of our timeline development, what we did, instead of kind of targeting those 3-year time periods, we assigned three to four labels to be updated every quarter. That way we could manage the 80-plus. So what this resulted in

is earlier than the FDA implementation timelines. We do have some that will still meet those timelines, but we just needed to spread it out because of the resource.

Labeling itself, we identified the functional experts within a given team or therapy area. We held kickoff meetings well in advance of the regulatory timings or the timings that we had set. And then we worked with each individual product team to revise labeling to ensure we were in compliance with the regulation and the guidance.

And I think it was Dr. Sahin's slide that talked about all the discussions and reviews and really focusing on the risk summary statements. It's very much similar in the sponsor segment. Like in the industry, we spend a lot of time looking at the data, summarizing it, and seeing what should be pulled out into that risk summary statement before we submit to FDA.

Some of this stuff I touched on, but I guess what I want to point out here is because it's so time consuming and it's happening over several years, there's a lot of ongoing education, because in industry, people move around on different teams, and so while they may have gotten the initial training or the initial blast of information, you're always getting new people joining teams. So labeling really had to continually provide education and training.

And then after we had a label revised or in a state that we thought was ready, I would review the label as a single

labeling point of contact so I could share experiences across different therapy areas, see what -- if there's anything I learned on another therapy area that could be brought in.

Also, all of the members of labeling would review non-GSK labels that had been approved so, you know, as months went by and more experience was gained, we would look at that to see if we could gain some experience with precedent language that FDA had approved, and also the disease state risk language for indications of interest.

So a really important thing about submissions, and I want to make sure people are aware of this, is when you submit a label to FDA, you have to support all the changes. And after the first few submissions, it was really clear that we needed a standardized supporting document template assigned to those revised sections.

This would then include all the data supporting the label changes, and also it gives FDA a real view of what we're basing our risk summaries on. It also went over the search strategies, the search strategies that we used for pregnancy, the search strategies that we used for lactation, so they could see what we're searching, compare it to their searches and see did we miss any data.

So I don't have specific FDA feedback from this tool, but it's worked internally well for us. And then another internal feature is it gave clear accountability for the functional

experts on the sections they needed to contribute to.

We talked about the training. What I wanted to just emphasize here is, again, the amount of time it took to do the searches and also review the data, determine whether or not that data, either internally or published, would come into the label.

Also, you have these historical content in the label that's already approved. Mapping out that historical content, which could be decades old, really put our archiving systems to the test. That was often difficult to find where some of that came from.

And then when we brought the information, when different functional experts brought the text to the team to discuss, sometimes there was differing interpretations of the data internally. And then anytime that changed, we had to always assess, well, does this impact our global risk statement in terms of our company core data sheet?

And then, of course, when we went to the FDA and we got their initial comments back -- and someone alluded to that negotiations with FDA, those can take several rounds. So we'll submit something, FDA comes back. We'll submit something else. It goes back and forth. So we had to come to resolution on differing interpretations of data, what data should be included, what shouldn't, like that.

In terms of standardization, we really tried to make our

searches standardized, and make our approach and our language -- so you've talked about the intro language. We tried to carry that through.

But as you know, there are, you know, about 16 different review divisions that are reviewing these labels, and oftentimes their preference or their differences and changes come back to us. And so we're not forced, but essentially, we need to go with the language that they recommend.

One thing I want to point out here: We talked about the time consuming and all the meetings internally. I will say it was a challenge for some of the older projects. Fewer resources are assigned to those. So we just needed to ramp up our resources for some of those, to make sure we had adequate folks from multiple disciplines.

And then one thing I want to point out here is GSK did all of our reviews, searches, reviews and writing internally. But I know that several sponsors had to outsource this work. So whether it was the searches themselves, the evaluation of the data, or the writing of the text for the label, this probably increases the complexity once you get to those negotiations with the FDA. And this is presumably due to those companies not having the expertise within, or just not the people to do the work.

I'm going to skip that slide.

Okay. Other sponsor insights. We've talked a lot about

data and what's published and putting it in labeling, but it was made very clear to us that not all data is appropriate for labeling. It needs to be robust and well designed. And some studies that we proposed were not accepted because different methodology was expected by the various review divisions.

So that was a learning. We still generally proposed more than less and let FDA come back and either take the information out, but we wanted to make sure we were including as much as possible that we thought was relevant.

We were able to align some of the labels with class language. That's addressed in the guidance, and FDA has approved that in some cases.

Across the different review divisions, I mentioned there's different thresholds for including the data. Generally, we've seen that limited information has been accepted in the clinical considerations section, or it was streamlined and only the best data was taken and kind of weaker data was excluded.

So I know that the Advisory Committee has questions that you're asked to answer. We also just have some questions that I wanted to put on this slide. Some of these align; some don't. We've seen a lot of differences from the different review divisions, and we haven't gotten a sense that a lot of consultations are done for the Division of Pediatric and Maternal Health. And we wanted to know if that would aid in the review process, if they could be consulted more

consistently. It seems, in the few cases where they were consulted, more relevant information seemed to be included in the label.

And then we've talked a lot about data and how to present data in there, what type of data. If there's any kind of standards around inclusion data that can be created to guide industry, I think that would be helpful, because we've struggled with that, and again, there's differences across review divisions that come back.

We've also been less successful in getting disease-specific rates on, say, birth defects and miscarriage in there, data not being robust enough to kind of compare to those general background rates of birth defects and miscarriage. So we wanted to know kind of what studies and what sources would produce acceptable data for that.

This is my last slide. That flew by. So we defined and agreed on a standard approach. We really had to focus on timelines because of the 80 products and not putting in 40 and 50 labels in one month. I'm sure FDA appreciates us staggering that as well because it is a lot of work on their part.

Updating labeling is a complicated process, and just in terms of all the timings over years of how this has been developed and the implementation timeline, it's not going to happen overnight. It's going to take a while. But I feel like we're making some serious progress in terms of getting

information out there.

We're trying to consistently apply the learnings we've made. We're getting better at evaluating data and supporting the data that we're including. I think my last point is there's just not enough data, human data, that is. And I think that we've all acknowledged that today. There needs to be more information to help healthcare professionals make better decisions.

So I will conclude there and take any questions.

DR. BLALOCK: Thank you very much.

Clarifying questions for Dr. Lee?

Dr. Berube.

DR. BERUBE: David Berube here.

I keep hearing calls for more data repeatedly, and I'm concerned about two things. First thing I'm concerned about is how do you -- how does the industry, as a sponsor, compensate for the decline effect, which is a prominent effect in the literature indicating that a vast majority of the studies that have been published can't be replicated?

I mean, Amgen reported recently that they looked at 53 research papers and tried to reproduce the findings and failed 9 times out of 10. And the search for more data seems to be challenged by this decline effect.

The second thing is I'm trying to figure out -- like everybody's been talking about ways of approaching the subject

matter. You hit on it as well. Has anyone done like an economic analysis on the desirability of investing limited resources in producing a whole generation of new data when we're not even convinced the new data's going to have a significant impact on how carriers and pregnant women will respond to the data?

DR. LEE: I mean, I don't know how to answer your question. I mean, I think that in other areas in labeling and getting labeling approved, there's data. So we're basing it on data. I think that, you know, having more exposure information would certainly provide us some more information.

DR. BERUBE: I did 2 years with the NSA on a grant to do data triage, right. And the one thing I know about is what happens when you have too much data. And I'm just, I just don't see the utility of generating a whole new era of data collection in the subject field until I am convinced that the new data we're going to be generating is relevant.

And as we in risk communication know, the majority of times it has nothing to do with the data, right. The messages that you design that are effective or not have very little to do with data. It has to do with a whole bunch of other things that the public and even experts respond to.

And I just, I'm just wondering has anyone like taken a step back and did this analysis, before we take a big step forward and invest a whole bunch of resources to produce just

another set of data? Sorry.

DR. BLALOCK: And, you know, since that's a clarifying question for the speaker, do you have a response or --

DR. LEE: I mean, generally, my feedback of wanting more data comes from OB/GYNs, so that they can make decisions in their patients. So maybe one of the FDA members who's, you know, in that discipline could comment. That's what I hear is that more data is needed, even with the individuals I work with on these teams in the company.

We're only able to put in the label what data we have. And if all those phrases, "inadequate," "not enough," "insufficient," "limited," if that's the first stance and that doesn't help anyone, I'm just suggesting, what do we do?

DR. BLALOCK: Okay. And I think Dr. Yao wants to comment as well.

DR. YAO: So if I'm hearing your question correctly, it is whether or not we have evaluated the need to collect any additional data at all, and whether or not those data would be helpful in making informed decisions in the use of drugs in pregnant women. If that's the question, then I would say resoundingly that the answer is that we need more data. I think that where we fall short, as we've heard, are in the adequacy of the data that are available and the methodologies that we use that give us more confidence.

So I don't think that the answer here would be that we

don't need more data. I think that the answer here is that we, and in other spheres that are working on the collection of clinically meaningful data in pregnancy and lactation, that you know, there are actively other groups that are looking at that. And I'm looking at Dr. Spong, too.

So that would be the first thing. The second thing I would say that, you know, in this issue of reproducibility of results and whether or not a study can be reproducible, I think that's a slightly different question. And I think that certainly at FDA, we have very strict regulatory standards that are required in terms of both study design -- sorry, all three areas, study design, study conduct, and reproducibility, and the issue of relating to need for adequate and well-controlled investigations, plural, to support an approval of a product.

So, in the regulatory space, I do feel like that we are getting information. And we're asking for information that will help us. In the area of pregnancy and lactation, I think that we can all strive to get to that quality. And in the meantime, we need to recognize the limitations that we have in the data that are being collected currently.

DR. BLALOCK: Thank you.

Dr. Winterstein.

DR. WINTERSTEIN: Yes. There were two commentaries this morning and now from you as well that talked about the lack of standardization in expressing information. And you commented,

while you were transitioning to the new labels, on your efforts to do so and the communication with the FDA, and there were several review divisions and so on. And, of course, the FDA on the other side has 18 or more manufacturers to work with, so obviously that standardization can become very difficult.

So as new information -- could you comment on when new information is emerging, what is your process of incorporating that new information, along the lines of standardization and keeping things up to date?

DR. LEE: So I thought that might come up because earlier there was a comment about industry updating labeling.

So it depends on the lifecycle of the product. And when they're newer, safety and pharmacovigilance, they're doing reviews every 6 months. And when they're identifying flags or risks, that gets progressed into the company core data sheet, and then it's rolled out into local labels, which the U.S. would be one of. When the products are older, I think it expands to 1 year in terms of the review by the safety group.

So I'm not generating that data, being in labeling, which is under the regulatory umbrella, but there are other disciplines within the company that are evaluating that.

DR. WINTERSTEIN: Yeah. That would be the first data, so the spontaneous adverse reaction data that you're talking about. But, you know, obviously you have divisions in your company that monitor any kind of safety information that

emerges around your drugs, and that could also be any type of other Phase IV type of study. Is there a mechanism that this information is reviewed and fed back somehow?

DR. LEE: My understanding is it includes published literature as well. So when they're searching to do their periodic safety update reports to give to health authorities, they are looking at all aspects of safety.

I'm not in GCSP, the clinical global safety and pharmacovigilance group, so I don't have a great knowledge of that, but that's my understanding of how it works.

I see some nodding heads, so I --

DR. BLALOCK: Dr. Nahum, you had a question for the speaker?

DR. NAHUM: Yeah. Actually it's a follow-up because I was going to ask something along the same lines.

But one of the things I think, and I wonder what your thoughts are on this, that is a little bit difficult, you just outlined that there are periodic internal reviews that are done at companies, and you said every 6 months or every year, depending on the maturity of a product. I think in some cases it's done more often than that.

But the question really always arises is when is new data enough to change a label? And we heard a presentation this morning, where with an antiepileptic product, the first data that came in suggested that there was a very, very high

relative risk, associated with its exposure, for fetal anomalies. And then later, as more data trickled in, it turned out it wasn't nearly that much, if at all.

And so really what we need -- this is what I'm asking -- is do we need guidance from FDA to be able to say when is enough of a change in the conclusion about safety data, especially in a benefit-risk format, sufficient to go about asking for a labeling change? And this is not something that's trivial. We have to wrestle with it with every product that we have.

DR. LEE: Was it to FDA or to me? It's a good point for discussion. I mean, I do know that we have received -- sponsors receive information requests from FDA to make updates and make changes to the label that they've identified that need to be done.

I think it is hard to determine, like that critical point where it's, like, okay, there's enough to change the risk-benefit profile. But, hopefully, safety groups within industry are evaluating that and they're looking at the totality of data. And when they do their searches, they're adding them to prior searches done. And when it gets to a certain level, that's when they make a decision. And it's not just for a U.S. label. It starts internally with a company core data sheet, the position, and then, you know, expands from there.

I will say that this U.S. regulation, though, has prompted

those other discussions internally. And while some of the background rates in the U.S. general population and the disease state rates don't make it into our global core data sheet because they're not relevant to other markets, we have re-looked at information and gone back and updated our company core position. So the U.S. is pushing us to like look at it. And we've made updates because we found new data as a part of adhering to the regulation, if that makes sense.

DR. BLALOCK: Dr. Pleasant, you have a question for Dr. Lee?

DR. PLEASANT: Yes. Thank you.

All this, essentially a lot of this goes back to clinical trial design. And so when you think about what the EU has done on the summary requirements for clinical trials and how that might create a feedback loop into the design of this trial, has this labeling requirement started a similar parallel conversation within industry when you look at the labeling requirement and say, hmm, maybe we need to rethink the way we're designing our clinical trials?

DR. LEE: Well, I think there's always an interest to do that. The POAP panel that I mentioned, the Pregnancy Outcomes Advisory Panel, they do inform teams of when it's appropriate or not appropriate to include women of childbearing potential and then what sort of precautionary methods need to be taken.

So I think that it's always being looked at, but maybe not

to the level it needs to be yet. I think it's a slow process.

DR. BLALOCK: And one final question for Dr. Lee from Dr. Goldman.

DR. GOLDMAN: Yes. This is Myla Goldman. I actually had more than one question written down, but I think maybe some of them might be more clarifying for the whole group to couch tomorrow's discussion.

But for you specifically, does GSK have -- it looks like you have pregnancy registries for some of your products. Other drugs that I'm familiar with have pregnancy registries. Can you speak to is there any requirement or precedent in how that data is reviewed and then reintegrated into the system? Are you just collecting it? Is every company doing it differently, because I would argue that we have all the data that we would need to inform lots of these discussions, because as was pointed out, we've been giving the flu vaccine to hundreds of thousands of women for years, but we don't have any way to harness that data.

So I'm curious, in this specific arena where we have all of these pharmaceutical companies that have all these registries, what's happening with that content?

DR. LEE: So I can't -- I don't recall all of the label examples, but I know, for example, Imitrex for migraine, we have enough exposures to sumatriptan that we have that pregnancy registry data now approved in the PLLR format. But

there are other pregnancy registries where we didn't have sufficient numbers of patients. And so we say there's limited numbers to make conclusions.

The real -- I mean, my -- what I've observed -- go ahead.

DR. GOLDMAN: What's that cutoff? What decides sufficient versus non-sufficient? Is that number available somewhere or --

DR. LEE: Well, in our discussions, it's been like a cutoff of around 300 and then 1,000 and then 3,000. Like there's been various cutoffs, depending. But if it's less than 100, we haven't put it in.

So I think you have to look at the registry itself, make sure they were all on a specific agent, and then determine if it's appropriate to include. And then FDA then determines whether or not they want to summarize that information there as well, when we submit it to them.

So I don't have any hard and fast numbers, but that's just coming to my head from like a general recall. We don't get as many pregnancy registry entries or outcomes as we would like, unfortunately.

DR. BLALOCK: And Dr. Spong has a very quick final question.

DR. SPONG: Just point of clarification based on the question from Dr. Pleasant. When you're updating these labels, are you doing clinical trials in pregnant women to get that

information, or is this just based on what information is available from registries?

DR. LEE: It's based on registries, published literature, and then spontaneous reports that we have in our safety database.

DR. SPONG: And do you routinely do -- does your industry routinely include pregnant women in these clinical trials?

DR. LEE: We don't routinely. No.

One more question. He's got his hand up.

DR. BLALOCK: I want to move on to sort of the next. And I see that Dr. Nahum has a question, so if we can get him first on the list.

Thank you, Dr. Lee.

DR. LEE: Okay. Thank you.

DR. NAHUM: Yeah. I'm sorry.

DR. BLALOCK: But wait just a second. Wait just a second.

We're a little bit ahead of schedule, so we're going to push things out of order just a little bit, push the break down. We'll get it. We're not deleting it. But we'll just push it down a little bit. And what we've actually got at 3:30, if you look at the agenda is another opportunity for clarifying questions. And this broadens it up a little bit.

So as I understand it, we can ask, you know, clarifying questions of any of the speakers this morning. So, again, they should be clarifying questions, because we're very close to

being able to really open up the gates and have discussion, but that will be after we get the charge from Ms. Duckhorn.

So clarifying questions for any of the speakers. And, you know, if in the question, you can identify the speaker that you'd like to address the question to, that would be great. And then if that person can up to the podium so that they have the mike, that would be great as well.

So, Dr. Nahum, thank you for your patience.

DR. NAHUM: Thank you. So Dr. Nahum.

One clarification on the last point that was made with the last speaker: The one thing that I think might have been inadvertently omitted is that there are Phase IV studies that are collected often in parallel cohort fashion that also weigh in to these types of ongoing safety assessments and benefit-risk assessments. And I think that was just inadvertently omitted, but maybe if the speaker could come back and clarify that, that would be useful.

DR. LEE: I think Dr. Sahin talked about those earlier, right. I don't have a lot of familiarity with those. We haven't seen -- in the labels that I've worked on, I haven't had results of those Phase IV studies described in that form or fashion, but my understanding is they do exist.

DR. BLALOCK: Thank you.

Dr. Goldman.

DR. GOLDMAN: So I have two questions that maybe relate,

are appropriate for one of our FDA representatives.

One is Dr. Lee mentioned about disease-specific risk and trying to find that. In that section of the labeling, who is the onus on to provide that information about what is the disease, the risk of the disease to pregnancy? Is it on the industry sponsor, or is it on the FDA? Where does that information come from?

DR. YAO: So, typically, we do ask the sponsor to provide any information they have that would populate all of those sections that apply. So we would ask the sponsor to provide information. But as Dr. Lee had mentioned, FDA performs its own independent review of the information that's available, to make sure that we are more often than not coming to some reasonable consistency about what those, you know, disease-specific considerations are.

DR. GOLDMAN: Oh, can I ask my second question?

So my second question sort of ties into that, which has to do with consistency.

So in several of the examples that were provided in the background section, that the language was different, so the details were the same, but the way the sentences were structured were different from one label to another. And I suspect, with this disease-specific, that also varies.

So is one of the discussion points to be around sort of the opportunity for consistency, or is that one of the things

we're supposed to be thinking about for tomorrow?

DR. NGUYEN: That input actually would be very helpful to us. I mean, we actually are very open-minded to suggestions you may have to improve the information that we have, acknowledging that the information we have is not the greatest quality. So if there are consistent/standard statements that you think will be helpful, we certainly would love to hear that.

We would also like to, I think, make aware that we try to fit these information under clean buckets, you know, I don't know, inconsistent results, limited results. They do fit in a bucket, but when you come down to each label, many times we actually have to tweak it to really make it work for that specific product.

As far as risk associated with specific diseases, I think that's one area where we could gain consistency. So it really varies on the different subsections of Section 8.

DR. BLALOCK: Dr. Dieckmann.

DR. DIECKMANN: Thank you. This is Nathan Dieckmann. My question's for the FDA.

My head is spinning a little bit with just thinking about all the risk communication work that could be applied to the labels. And I keep coming back to trying to get clarification on exactly what the goal of the labels are and whether the intention is really to be a tool that would be used at point of

care.

So we've seen some examples of other web systems, TERIS and so on, that if I was a busy practicing clinician, I would certainly probably go to that TERIS system that showed me very quickly the level of evidence that's available and whether that risk can be estimated at all, as opposed to going to the label.

But we've also learned there's a lot of other legal requirements that should be communicated. So I guess I'm looking for, as we're all going to go down the rabbit hole soon in giving you like recommendations on exactly how to change the labels around, just more clarification on exactly what the goals are or maybe a range of the different uses, just to kind of help target our recommendations.

DR. NGUYEN: Thank you for those questions. I think they're really important questions.

So your first question is, is the labeling intended to be used by prescribers at point of care? We hope so, but we also understand it is a relatively cumbersome tool for a busy practitioner. But we certainly would hope that would be a popular source, so to speak.

Certainly, that's why the PLR and now the PLLR changes were done, so to make it more useful to prescribers. That's why we have the half-page highlights summary. So that answer is yes, we do intend it to be used at the point of care.

The second thing that I will mention is that we certainly

are aware of many other sources of information that's easier to use that gets you sort of like the end game statement, but recognize that a lot of those sources actually get their original information from the prescribing information. And they might modify it for certain types of prescribers and what have you.

And, thirdly, the prescribing information is not intended to be clinical guidelines. So I think that's where its limitation, so to speak, is to a practicing clinician, because clinicians like set guidelines. And that's why we have professional societies weigh in and what have you, but they too rely on information that's in the prescribing information.

DR. BLALOCK: Dr. Lyerly.

DR. LYERLY: Thank you. I just wanted to follow up on Dr. Spong's question to Dr. Lee.

So in your trials with women of childbearing potential, obviously there are going to be some inadvertent pregnancies which are sometimes relied heavily on as a source of data for the safety of drugs and vaccines in pregnancy. And I was just wondering if you are collecting those data, and maybe for the FDA, if there is some avenue for those data on inadvertent exposures in trials to get to the label.

DR. LEE: So we are collecting those data, but I think what typically happens is drug therapy is stopped after the exposure. But we collect those data, and they become a part of

our internal safety databases. But if they're not sufficient quantity, so it's a handful, it's not moving into the label because it's not enough to be helpful. But the outcomes or the follow-ups are collected.

DR. LYERLY: So when you offered the numbers for the registry, sort of thresholds, do you have different thresholds for inadvertent exposures that you deem relevant, or how do you think about that?

DR. LEE: Well, because the inadvertent exposures aren't intended and they're inadvertent, I don't think that we are hoping to get those and collecting it to a certain number. But I would suspect that if you got hundreds or thousands, it would be a similar approach. But I don't think it happens because of the pregnancy prevention guidelines that we put in place.

So the numbers that I quoted were more for pregnancy registry once it's approved, out on the market, and you're collecting those outcomes.

DR. LYERLY: Okay. Thank you.

DR. BLALOCK: Dr. Coombs.

DR. COOMBS: Yeah. I want to go back to earlier today with Dr. Namazy.

When you were talking about the information from the physicians and their reactions, kind of in the results and the values section, did you say something along the lines that this did lead to more discussion of risk and benefits with the

patient, with this new type of labeling?

DR. NAMAZY: No, no. What I -- sorry. I didn't have that part on the slide. I kind of mentioned it at the end of the slide. But I think that was talking about when we asked the responders, based on reading, after reading the narrative summary, would you use drug ABC? Fifty-three, I think it was 53% said that they would, or that they would use it but they would have to really consider the risk-benefit.

DR. COOMBS: Okay.

DR. NAMAZY: So there were a lot of comments just kind of talking about risk-benefit with the patient. And that just kept coming up, so that's what I wanted to put out there.

DR. BLALOCK: Dr. Lee.

DR. LEE: Two quick questions for the FDA folks; one is a follow-up to Dr. Goldman's question about standardizing phrases. When the sponsor edits the label, do you guys, are you guys able to just go ahead and edit as you wish, or does it have to go back to the sponsor?

DR. NGUYEN: So, in most circumstances, there's certainly a limited number of circumstances where we, quote/unquote, "dictate" the language. But in most instances, it's actually negotiations back and forth, with the final language being approved by FDA. But certainly during that, during those negotiations, FDA does provide its own edits and there is rationale provided.

DR. LEE: Okay. And the second quick question is have you thought about pulling out some of the absolute risk information into a separate, searchable database form outside the narrative so that, you know, technology companies can leverage that to represent information graphically and compare it against baseline? So is there a thought about how that could be made available?

DR. NGUYEN: So I think this goes back to why we need more data. Data is a four-letter word, so it could be good or bad. But, certainly, what we strive to have is reliable data. So we would not want to publish, be it relative risk, absolutely risk numbers, unless we felt some level of confidence in those numbers, and our state of science right now is that we're not very confident in most of those numbers.

So we would love to be able to generate a database like that, but the information populating that database is missing.

DR. YAO: Just to add onto Dr. Nguyen's comments, and I think Professor Conover said it very nicely too, which is that, you know, her patients or her or the prescribers that go to her for advice are saying, come on, just tell me what the code is.

So we have been very, very conscious of the fact that we want to provide standardization when we can and want to describe the nuance that we can, but we don't want to create just another lexicon that anything FDA says this, that just means A, anything FDA says that, it just means B. So that's

the part that's hard, and that's kind of the part where we'd like to get more conversation tomorrow.

DR. BLALOCK: Ms. Robotti.

MS. ROBOTTI: Thank you. I guess this is for the FDA.

The package insert that -- the information that we're talking about today is really targeted towards the physician. Where is the patient supposed to get their information from? They take the ultimate risk and hope for the ultimate benefit. But it's written in language you cannot expect them to understand.

DR. NGUYEN: So as we mentioned a little earlier this morning, many prescribing information comes with a medication guide, which is really written for the patient. And the patient would typically receive this when she receives her prescription. Or another documents that might accompany the prescribing information is what's called a patient information leaflet. So that's really sort of part of FDA-approved labeling, and those documents are written for the patient.

Now, the second component, and this is really important, is that the patient has her physician to counsel her, and there is expectation that there'll be counseling between the patient and the physician. So that's sort of the regulatory paradigm of prescription drugs. It doesn't explain the universe of information where the patient gets her information.

MS. ROBOTTI: And so the medication guides, is the

phrasing used within those guides, is that within the purview of this Panel today?

DR. NGUYEN: It is. So the medication guide is actually part of FDA-approved labeling. So in the most sort of concise way, you have the prescribing information, and it would have a medication guide accompanying the prescribing information. And those are all -- they have to be FDA approved.

DR. YAO: Can I just clarify, ask the question? Are you asking if what we're asking advice on, as part of this Advisory Committee, what you want us to be able to tell patients?

MS. ROBOTTI: Yeah.

DR. YAO: So I guess the short answer would be not so much. I mean, we do in the context of wherever you think it might be important in the PI, for example, if you have specific comments about medication guide. But we really, we've got a big task in front of us, the rest of today and tomorrow to talk about what we're putting in prescriber information. So that's really what we want the Committee to focus on.

DR. BLALOCK: Dr. Rimal.

DR. RIMAL: Thank you. I actually had another question, but I wanted to follow up with what was just said.

The patient information leaflet, the patient has access to that only if she's given the -- she decides to take the medication prescription, right. Otherwise, there's no other way for her to get that information.

DR. NGUYEN: Yeah. Actually, if you go to certain searchable databases -- FDA's is Drugs@FDA -- you should have accessed to FDA-approved labeling. And often you'll see the medication guide or the patient information leaflet with that information.

And, actually, while I'm at it, I will clarify that the documents that are for the patient contains the information that's in the prescribing information. It's written in patient-friendly language, but it certainly contains the information that's most important for the patient to safely and effectively use a drug.

DR. YAO: We would be happy, if the Committee would like, during the break to pull up an example or two of what that looks like.

DR. RIMAL: If you don't mind. So I'm reflecting back on the conversation we had this morning about how to effectively communicate risk information. And much of that focused on the presentation format, you know; do we talk about the numerator, the denominator, percentages, etc., etc.

To me, what was missing from that discussion was anything to do with the receiver characteristics of that information. So we know, for example, there's a whole group of people in this country who feel very disenfranchised, whose trust towards the medical system is very low and therefore are not likely to receive that information in -- or they're likely to receive the

information in a certain light.

So when we talk about labeling, I have some discomfort with the fact that we're focusing exclusively on the language and how it is framed. And there is nothing there about the patient himself or herself. And, you know, I think it's a tension between, on the one hand, standardization of the information we provide, which many people have talked about, and on the other hand, personalization of that information so that it's palatable to the particular person you're targeting.

So I guess there's a broader question to the FDA in terms of our charge, and I guess to Jodi, before we get that charge, is there any room for having some recommendation for at least understanding some aspect of the patient as a requirement in the language that we present?

DR. NGUYEN: So I think you hit on a really good point of the limitations of what we can do with the prescribing information. And I know it sounds like we're very focused on a document, but certainly its intention is to contain all the information that will assure the safe and effective use of a drug. It is information. It is for the general audience consumption. It is certainly not designed to able to individualize to a certain patient based on her unique risk-benefit balance.

And so I think I just want to be very clear that this is what I like to call a general information document. And then

you have the prescriber, who's going to help translate that for the individual woman and have that dialogue with her and incorporate her values, you know, her risk tolerance and what have you. So that really is done on that patient-prescriber relationship side.

So I hope that helps clarify the limits of what we can do with prescribing information.

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thank you.

My comment, clarifying question is really to Dr. Wisner and maybe a little bit to Dr. Riley, and it flows directly from this conversation we're having.

Dr. Wisner provided a wonderful example of how she counsels patients and how she takes information, and is looking at both the condition that the patient has as well as the medication that might be useful and that whole counseling around that description.

And I guess I'd like to have a little clarification from her of, you know, how long does that take? How is she able to do that, knowing when I see a patient, I don't have, I think, enough time to be able to get done what's describing in the current confines of how they're set up. And how might what we provide in this document be able to assist that, so as to allow us to be able to give that information in the time constraint environment in which we live?

DR. WISNER: Yeah. It's a good question. In the environment I work in, which is an academic, psychiatric consultation service, it usually takes me about 45 minutes to an hour to do an assessment like that. And it potentially could take longer, except that I do some of what I was talking about in the presentation as well, which is I look through her medical record and I get information on the new drugs I'm not entirely familiar with and I get all my materials that I'm going to hand out in advance.

So it does take a fair amount of preparation. So, yeah, it takes a while. How could it be shorter? Well, I keep thinking again about this New York model where you have all that information in advance and somebody else pulls together the information for you, because it really helps to have some sense of the information about a particular drug and disease in hand before you go talk to the patient, because it helps focus your questions for the patient and the assessment of her disease state as well.

Sometimes, if I have a real limited amount of time, what I'll do is do the assessment and set up a series of questions that we'll answer in a phone call later. And sometimes that's necessary because the patient has a lot of decisional conflict and can't really make a choice at that time and wants to talk to her significant others. So you're right, it is time consuming.

DR. BLALOCK: Dr. Yao, you have a response as well?

DR. YAO: I do. And I think, just to clarify and to ask the Committee to think about it as we move forward into our discussion questions tomorrow, on my Slide 6, if you want to take a look at that again, that slide says that the labeling is for a summary of essential scientific information needed for the safe and effective use of the drug that is written for the healthcare provider, that it must be informative, accurate, and neither promotional in tone nor false or misleading, and it must be updated when new information become available.

So that's sort of the low bar, right. That's the minimum that labeling should achieve. However, having said that, in any way that the labeling can be improved such that it's a better tool when you're busy and there's little time, or that you are coming up against cultural, you know, longstanding societal issues that you think this document could be improved upon, that's exactly the kind of advice we're looking for.

DR. BLALOCK: Dr. Kreps.

DR. KREPS: You know, I've been listening to the conversation all day, and I'm -- you know, this is something that I'm kind of confused about, so I'm hoping that my friends from the FDA, Christine and Lynne, can help me with.

It seems that you want a clarification on how to develop the labeling message, but I'm not sure if it's clear what the information is that you want to present. So we've heard this,

you know, common phrase about we need more data, but it sounds like the data that you currently have is equivocal. It's hard to understand, and it's not consistent.

And I wonder if there's a -- you may already be doing this, but I wonder if there's kind of a review to evaluate what are the strengths of the data, what do we know, what do we don't know, and what are the conclusions that we can reach? It's extremely difficult to come up with a good message when you're not sure what it is that you want to present.

And it sounds like, from some of the sample messages, label messages, the messages themselves are confusing because they're not clear recommendations. And so maybe, you know, a step before, you know, standardizing the labels would be to step back and say how do we clarify what it is that we know? And what are the lessons learned? What do we want to recommend in terms of the strength of the evidence? And how do we clarify that? Because once you have a clearer sense of what it is you want to communicate, then I think it becomes much easier to develop a really good set of messages. But without that information, it's very challenging.

DR. BLALOCK: Dr. Goldman.

DR. GOLDMAN: My question was related to the -- for the FDA. How does this work, then, for generics and biosimilars where, you know -- just as a point of understanding, do they carry the original label, or how does that happen?

DR. YAO: Right. So, for generics, that's a pretty easy answer. Generics that are prescription fall under the same requirements under PLLR. So the reference product labeling, if that's an NDA, which is, you know, our regulatory term, if there's a drug that's still a holder of the labeling, all the generics will be required to fall after that.

And if it's a generic that's the reference product, they have to change their labeling, and then all the generics have to go. For biologics and biosimilars, it's the same. Anything that's prescription product falls under PLLR if it was approved after 2001, and then some of the other rules that we talked about.

DR. GOLDMAN: What I mean is does each individual pharmacologic entity need its own PI?

DR. YAO: So they all do, and generics follow very closely. They have to contain the same labeling as the reference product. So that's fairly easy to convert. I should say easy -- I'm not -- I don't work in generics, so I'm sure it's not that easy. But, you know, all of those labelings have to --

DR. GOLDMAN: The manufacturer of that generic is also submitting the PI.

DR. YAO: No, they are not, generally not. They will follow whatever reference product has submitted their labeling change.

DR. GOLDMAN: Got it.

DR. YAO: And then all the -- then the generics have to change their labeling to be the same. There's no negotiation there really.

Biosimilars are slightly different, but we haven't gotten to the point where we have -- you know, the biosimilars were negotiating those new labelings anyway, so --

DR. KREPS: Re-address, I get the --

DR. BLALOCK: Sure. And -- but make the, you know, make the question, you know --

DR. KREPS: All right. So the --

DR. BLALOCK: Clarify what the question is.

DR. KREPS: The question I had was basically about data reduction. Is there a need to try and clarify what it is you want to say, and is there a method for doing that?

DR. NGUYEN: So if I think -- if I may rephrase your question and make sure we can answer it for you, is that present -- in the present, we have data/information that's very nebulous. You know, you can tell by a labeling there's a lot of, well, it shows this, we kind of don't know, and you know, that's all we can say, right.

We're not saying don't take it, take it, take it with caution, or anything. And your question is given that circumstance, FDA go back, figure out what you want to say based on your review of the information and figure that out,

and then perhaps we can help you. Am I understanding that correctly?

DR. KREPS: Yeah. I'm basically saying, figure out, you know, where the findings are relatively clear. There are some cases, I'm sure there are, that you have some clear evidence, but there are probably many where they're not. So identify where you have the strongest evidence and put that in a group where you're ready to go for messages.

Identify the ones where the messages are not clear. You may need to clarify and follow up and then direct that type of effort to get better information. Because the better the findings are, the stronger the findings are, the better able you will be to come up with meaningful labels.

And so, you know, maybe this is not the case. Maybe all the information is clear and that's not the problem, but that's not what I've been hearing.

DR. NGUYEN: So I think the bad news is that we don't have clear information. So the labeling that you see is the best that we could do right now. We combed through multiple sources of data. We threw out information that we thought, well, you know, really, we're not going to include that in labeling. And believe it or not, the information we put in labeling is what is the best available.

And what we're struggling, and that's why we're having this panel today is, is this helpful in any way? We have to

put in best available information. The law requires that we do it. We can't wait until we have clear data before we put it in the labeling. So given our current conundrum and situation, how do we best do it?

So you're confused, and I think it reflects, you know, the struggles that we have on this end. And so we're trying to get your input in terms of how we can best do this, given the very imperfect situation that we're in.

DR. BLALOCK: And it looks like Dr. Yao wants to respond, but I also want to comment that actually what I'm hearing more is a recommendation from you rather than a question. And we're going to have lots of time for that, but I also have a sense of maybe moving on to clarifying questions.

But, Dr. Yao, it looks like you're jumping, wanting to respond.

DR. YAO: Yeah. I just want to say one thing, which I agree actually, Dr. Blalock, completely with what you've just said. And I just want to remind the Panelists, because we've got, you know, just the tenor of the conversations, the questions that are being asked already give me great hope that we're going to have a very important outcome from this meeting, which are recommendations that will help us.

But to your point, Dr. Kreps, what we have -- what we had historically in labeling is more or less exactly the same as what we have now, except for we removed that letter. And now

everybody thinks that everything has been changed.

The effort that we've been making is to provide more information because we felt like the letters were not doing the trick. And we had lots and lots of advice and input previously that said these letters weren't really telling the full story.

So as we're moving away from that, we've been trying to do our best to describe these nuances, to describe the inconsistencies when we've had them, the conflicting information when we've had it, and then the lack of information when we've had it, and in the very, very rare circumstance where it's been more or less easy, when we had a clear signal that was easy to write and that people knew.

So what we're trying to do is construct a way -- we've constructed some examples that we'll go over and discuss again tomorrow, but to get your advice about how do you describe that, those nuances in a way that doesn't need to another letter categorization and that we hope fills that void that prescribers want, which is this perception that those letters were helping us.

DR. BLALOCK: And I've got, you know, quite a long list of folks who have questions, and I think we're going to have time for, to get around. But just again, you know, asking for everyone to keep them to, you know, short clarifying questions, and then we'll get to discussion and recommendation very soon.

So the next person on my list is Dr. Wolf.

DR. WOLF: And I think I don't want to repeat too much about -- Gary, I completely feel your pain, and I feel yours.

The question, I guess, is what is your outcome? Is your outcome -- and this is what I've been wrestling with, and if it's denied, but is the outcome that you're dealing with prescribers who have to deal with treatment uncertainty, which I get, because you're not going to answer it until the data comes in?

And I actually do agree with everything you said. You need more data. Yes, it's a good or bad word, whatever you want to get into. But are you looking to see, to kind of either assist prescribers in getting through that uncertainty because it's not going to go away?

And if that's the issue, versus just the messaging, I just want to make sure that I understand. This is a true clarifying question. If our job, as this Committee, is to figure out how best to convey in a manner the uncertainty around the data that we have as to what to move forward with, because you're not looking to see -- based on the evidence, you don't have the -- to know with any specific patient that they did the right thing or not in that particular case. Is that -- you're just trying to make sure that you can convey, as best as possible, we don't know?

And the next level would be -- and I didn't know, with the PLLR -- I'm more familiar with the PI -- that you had, since

2006, you had guidance that would include patient counseling. I think that's when it first kicked in that you were supposed to provide some guidance that I don't think probably many prescribers use, mostly because there's kind of a disconnect between how that material actually gets into the flow of patient care that Dr. Dieckmann kind of raised.

But is that also part of it? Is there opportunity that you also are trying to figure out how to not only address the reconciliation of the uncertainty but also how they might communicate that to patients? Does that make sense? Because that used to be part of the PI.

And I don't know if that -- there used to be some section that was supposed to provide some words, you know, based on all this stuff on clinical trials, what you've learned, animal, whatever you want to get into, that boil it down, these are the three or four things you should tell patients when you're ordering this med.

DR. NGUYEN: So I'll apologize. I'll clarify that. So the PLLR is actually a part of PLR; it just -- it's been delayed intentionally for that gap. So to answer your question, yes, we would really like to hear your input on how we can present the information in pregnancy in a way that can be interpreted by the prescribers. We are not removing uncertainties because they are what they are. You have a black sheep, you have a black sheep. You're not going to remove the

blackness of it.

So yes, how do we best communicate uncertainties in the way that really can be translated by prescribers so that they can use the information, as opposed to reading it and saying, I have no idea what confounders mean, for example.

We are also looking for input so that we can give information away that doesn't tie a prescriber's hand. So we hear a lot about, you know, don't be too prescriptive, FDA, because you tie our hands. We may have a patient or two who really needs this. So we like to make sure we're not doing that under appropriate circumstances. Now, if they're clear risks, we're going to communicate that they're clear risks. So that's the second part of it.

As far as the patient counseling section I think that you're referring to, it's the last section that's in the PI, yes. So there are some regulations that dictate what we put in the patient counseling information. And if the pregnancy-related information meets the criteria to put it in patient counseling, we will put it in there.

But, again, if you have pretty neutral risk information in a pregnancy, that's not something we're going to carry over into Section 17. Section 17 is a little more what I call active counseling. For example, the patient needs to avoid certain medications, if she has to take it with food, if she -- you know, if there's active counseling that must be done, then

that's usually included in Section 17, but not everything. There are criteria that dictates what we put in there.

DR. WOLF: Just to clarify, so you wouldn't -- this is helpful to know. So you would not put information in this, in the instance, in patient counseling section, on how to explain to a patient why they shouldn't be on this medication if -- or if you chose to, we're going to proceed, but we don't know?

DR. YAO: So, generally, the patient counseling section includes information that has been described in other sections of labeling to the prescriber that are -- that we want to make sure the prescriber communicates. So those usually land in the area of warnings and precautions, do not use -- you know, advise the patient to use contraception, those kinds of things, which don't lend themselves to the conversation of what we want to put in 8.1 when we're not sure what the risk really is.

So I would say then, in general, that kind of conversation would likely be limited to Section 8.1 and not necessarily, you know, bleed if you will into Section 17, because it might sort of change the important messaging we want to get across in 17. Does that make sense?

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: Dr. Joniak-Grant. I had a question.

The goal here is that we want the labels to work better and to be used by the healthcare provider, right? And, Dr. Namazy, correct me if I'm wrong, but you -- I believe that

you intimated that the providers were more likely to use the label if they felt it would be -- was in a sort of patient-friendly format, easy to digest, they could get through it on a busy day and sort of move on.

DR. NAMAZY: Well, the question didn't get that specific. Basically, the question was do you use the pregnancy labeling system, pregnancy label to make decisions? And 73% said yes, but there was, you know, other outlets where clinicians do look, such as UpToDate and Lexicomp, other places that we had said. But 73% said that they do use the label when deciding to use a medication.

DR. JONIAK-GRANT: Because I guess I was looking at the slide that said what's next --

DR. NAMAZY: Oh. Will you pull that one up?

DR. JONIAK-GRANT: -- which suggested that many clinicians lack the time to navigate through information and present it in a clear way to their patients. So would having a label be written in a clear way for patients help deal with this issue?

DR. NAMAZY: Absolutely. Twenty-nine percent and forty-nine percent didn't think that it was clear or concise. So that lends you to believe that maybe it needs to be a little bit more clear and concise. I think that's why I put that last statement in.

DR. JONIAK-GRANT: Okay. Thank you. And then with that, I guess I don't see why that's sort of counterintuitive to be

mindful of what would help, what would be patient-friendly speech. I feel like it's sort of being presented as healthcare provider world, patient provider world, rather than, well, if we made it friendlier for patients, we're also making it friendlier for the healthcare providers.

And along with that, sort of this notion that -- this notion that patients can just go ask their doctor is -- I think really doesn't recognize that everybody has access in a timely way or financially. The medication guide generally has very little information that's useful for anything more than, you know, how many times a day should I take it, do I take it with food or not?

And so I guess I see the benefit of putting it in patient-friendly terms on all these things. I don't see where there's not a benefit. And so I'm just kind of puzzled why there's such this strong bifurcation.

DR. YAO: Yeah. If I could use an example to help maybe describe what the difference is, which I understand exactly what you're trying to say. And please don't take that what we're saying is that because the labeling is intended for the prescriber, that we don't want it as clear as possible for the patient.

But if we take the example -- and I think this might help -- of the difference between labeling in a prescription product, which we, you know, understand under, you know, law

that a prescriber that is licensed to practice in whatever jurisdiction is the one that must write for that drug, right, versus something that appears over the counter.

So over-the-counter labeling is a very different beast than prescription product labeling, and I would, you know, point you to the drug facts label, which is the title that we give to over-the-counter labeling, which very much is absolutely intended for the consumer.

And that type of labeling is fundamentally written in a different way than what is written for prescription product labeling. So that gives you, I think, a flavor of what we mean in terms of the difference.

Having said that though, again, I appreciate your point, and we're not saying that we don't want information that's, you know -- that can be unclear and imprecise, because we're going to give it to prescribers who must understand this all and then can translate it to, you know, patients.

We understand that patients are going to read this information too, so we do want it -- we also understand that the information that's taken from labeling, prescription product labeling, often gets turned into -- right, digested in some way and then turned into information that patients will read directly. So we want to make sure it's as clear as possible so that translation doesn't get messed up either.

DR. BLALOCK: Dr. Berube.

DR. BERUBE: This is for you, for the FDA. Dr. Berube here.

Now that I know that the primary audience we're dealing with is prescribers, then all this innumeracy thing confused the hell out of me because prescribers should be able to do basic counting, right. I mean they're mathematically competent. So I'm not concerned that -- well, more than the general public, all right.

The reality is that these experts have other problems; they have other heuristic problems. There's this thing called the egocentric bias, where if you tell them too much, they back off, right. And you mentioned that to us. There's the other bias, which is the risk-aversive bias, which is that they want you to tell them, with incredible clarity, what the risk is.

Tell me if I'm heading in the right direction. You want us to help you find the sweet spot between the ego-aversiveness where you're telling them too much and the risk-aversiveness where you're not telling them enough. Is that where we're heading?

DR. YAO: I think those are all very valid points in what we might want to discuss tomorrow about when we have a statement that, understand FDA, that that may make the prescriber who is risk-averse or the patient who's risk-averse not -- what is that consequence for including it this way?

So yes. That's the kind of information we'd like to hear,

but I'm not sure that in any case, you know, we're going to get -- that there is a, you know, sweet spot for all drugs, for every indication, for every patient and for every provider.

DR. BERUBE: You're probably correct.

DR. BLALOCK: Dr. Sneed.

DR. SNEED: I think it's pretty much been covered, but in your Slide 6, you talk about healthcare provider, and then you talk about prescriber. Is that meant to be the same thing?

DR. YAO: Thank you for the clarification. So, you know, we know that prescribers now, you know, are not just physicians, and some healthcare providers aren't prescribers, but we're really talking about prescribers.

DR. SNEED: Okay. So it sounds like, to me, that the purpose of this is to help a prescriber decide whether that medication is appropriate for this pregnant or lactating woman, because then if you're talking about the whole counseling thing, then they may not be getting the counseling from that prescriber because most prescribers don't have 45 minutes.

And then, also, there's the intimidation factor that people feel around doctors. And so they may ask their pharmacist, or they may ask the nurse or someone else for information, for clarification. So it seems like there are multiple audiences going on.

DR. BLALOCK: Dr. Tracy.

DR. TRACY: Jim Tracy. I'm still also kind of wrapping my

head around this labeling thing too, a little bit, and part of what our charge here is going to be.

You know, we've spent a lot of time talking about communication of risk of using something. And it's been touched on by several of our speakers. And I keep getting kind of consumed by the risk of not doing something sometimes. We've touched on that. And I'm not sure where that falls into the labeling. Is that part of the discussion piece?

You know, we've spent really the majority of this time talking about kind of the down side of using these things. But, you know, a lot of times there's a down side of not using these things, too. And I think if we're going to be looking at the labeling as a whole, maybe this is a discussion point, but I'm not sure how we wrap our heads around that.

And I've been kind of struggling. Several of the speakers -- Dr. Namazy started it, and then Ms. Belsito really kind of pounded it home with a lot of her anecdotes. And so will the discussion piece -- I guess this is my question -- be a part of that? Or can that be a part of that?

DR. YAO: Yes.

DR. BLALOCK: That was Dr. Yao saying yes.

DR. TRACY: Thank you.

DR. BLALOCK: Dr. Howlett.

DR. HOWLETT: Thank you. This is Elizabeth Howlett.

I'm also following up on Dr. Kreps's point that I think is

really important, and that is I think we have a situation of a classic information overload, and we have a lot of information that we want to try to present. And not only is the presentation of that information very ambiguous, the information itself is ambiguous.

And so the question I'm asking, and point of clarification of, what kind of options are you open for to try to increase the clarity of the ambiguous information? For example, just came to mind, when I was working with the Institute of Medicine on helping consumers interpret a sodium level, you know, they had no idea, you know, is 1,000 mg good or bad?

And so we came up with a sort of a star system. So here's the quality of the survey. This survey is a three-star survey. This star is a four-star survey. So you could look at this and see, well, you know, the strength of the evidence across -- so are you open to other kinds of methods?

DR. NGUYEN: This is Christine Nguyen. The answer is yes.

DR. BLALOCK: Dr. Winterstein.

DR. WINTERSTEIN: I guess I still would like to clarify a little bit what the question really is. There were a lot of presentations and also a lot of questions about patient counseling and how the information is getting to the patient, and I wanted to review what information patients actually have.

There was a question whether they can get the label. Now, the label is on a database called DailyMed that is maintained

by the National Library of Medicine, and if patients knew that, then they would find them there. And if it's a brand drug that they got prescribed, they would also find it likely on the manufacturer's website.

But that's the only way they would find it, and many patients probably wouldn't. So what they would have is typically something that's called consumer medication information, which is actually a mandate for pharmacies to dispense. And this is the only time in the whole process that a patient gets cared for that they get any written information that is a pharmacy obligation to do.

We did a study more than 10 years ago that looked at the quality of this information, and the amount of information that is dispensed ranges from about 50 words to up to 5,000 words, which tells us that the quality of that information might vary quite a bit.

So this is the information that the patient would have available unless there is a medication guide. And I think it's very important to recognize that medication guides communicate a very specific risk. And then the question of teratogenicity of pregnancy, that would only be available if there were already a confirmed risk about a pregnancy issue. Otherwise, there is no medication guide that will talk about a pregnancy problem.

So, basically, the label -- the leaflet or the package

insert that we are talking right now about is nothing that patients have. And I would be extremely surprised if it were used typically anywhere, in a pharmacy or in a physician's office, to communicate any information to a patient.

So at the end of the day, I think it is essentially a legal document, we know that, and perhaps a scientific document that communicates information to prescribers. And if this is the patient -- and if this is the question that we are trying to answer here, you know, how can we make that communication better, I think that's an important question.

But I think we should focus that question on exactly that and not on something that has to do with communicating to patients. And I just -- so this is my clarifying question: Is this really the question that we're here to answer, because then let's forget about the patient for a moment and really talk about how do we structure the PI better so that physicians get the information they need in order communicate that fact or not. Does that make sense?

DR. BLALOCK: Yeah. Let me interject for just a minute because I think, you know, Ms. Duckhorn is going to come up, you know, after we take the break, and she'll be giving us the charge. And I would think, as part of doing that charge, that we'll have an opportunity to ask questions specifically about the charge.

Is that true?

Okay. So I'm getting a nod. So thank you for the question. And we'll pick it up when we're getting the charge.

Now, I've still got about five more folks on my list here. And these should be questions for the speakers, including the two FDA speakers. But let us do hold questions that relate specifically to the charge until we come back after the break.

So Dr. Goldman.

Dr. Slovic?

DR. SLOVIC: I was just going to respond to a question that -- it came up with regard to something that Dr. Kreps said, but it was a while back, and I think it's not really --

DR. BLALOCK: Okay. Maybe again, responding to the comments made by other Committee members, that's really best left for the discussion.

DR. SLOVIC: Yeah.

DR. BLALOCK: So this is truly questions for the speakers. You can tell I need fresh soda.

(Laughter.)

DR. SLOVIC: Well, let me just phrase it with regard to the very interesting survey that Dr. Namazy presented this morning. And then a question came up, and there seemed to be an inconsistency between the question, which asked, did you use this labeling information; 73% said yes. But they seemed to prefer the letters. So if they used it, why do they prefer the letters?

Well, I think I've had some experience with this question about what's it mean when you ask someone if you used information. We don't necessarily know what, how we're -- if or how we're using information. My sense was probably the answer that you got there was based on the fact that people may have looked at the information at some time, you know, a little bit, they glanced at it, they saw something in it that was interesting.

That doesn't mean -- you know, that's the tip of the iceberg with regard to using the information. I think the only way to know how adequate the use of the information is, is to test it, you know, to run these things by people and listen to them as they think out loud about how they are taking in that information and doing something with it.

And then you'll find out the extent to which people are using it, whether different people use it in different ways or adequate or inadequate ways. Just looking at a piece of information doesn't mean that you're using it.

DR. NAMAZY: I completely agree. I mean, I think that that was a little bit vague, that first question. Sure. I mean, they may have looked at the PI at some point. But I think what kind of came down to it, though, in the survey is that a lot of the clinicians still revert to the pregnancy categories, and when faced with the sample narrative, they still would have a hard time navigating to it and go back to

the letter category system.

DR. BLALOCK: Thank you. Two more questions before the break.

Dr. Cappella.

DR. CAPPELLA: I didn't have any clarifications. I only had suggestions, so I withdraw.

DR. BLALOCK: Okay. And Dr. Lyerly.

DR. LYERLY: So I have a question for the FDA, and I think it arose during Dr. Sahin's talk, when she was going through the labeling, the example labels, and was talking about the fact, I think, that there -- these were examples of labels that did not show a major teratogenic effect.

And I guess what my question is, is whether you could offer a little bit more information about how you think about what that threshold for a major teratogenic effect is, and then how you think about the role of reporting data that suggests a teratogenic effect in one direction or not and putting it up against a statement that it basically doesn't meet the threshold for clinical relevance in some way.

So I guess I would just like to hear more about how you think about that space of not yet teratogenic effect, and when is it that you get there and communicate that.

DR. YAO: We can provide -- I think I heard that there were maybe two things we could provide examples for after the break. The first was -- and I forgot already. A medication

guide, right. We can provide an example of Section 17, which is patient counseling information and medication guide.

The second thing I think we could help with, at least to give some -- I don't think it'll answer your question all completely, Dr. Lyerly, but an example of when we are convinced there is a teratogenic effect, how do we describe that? And how does that differ potentially from what, the other examples we've provided?

And I might also say that the labeling as a clear teratogen with warnings and precautions, maybe even a REMS on occasion, actually may not even necessarily be based on what we know to be, you know, be derived from human data. It may be from something earlier, and a clear effect, you know, in animal toxicology studies that would lead us to that. So we can definitely provide a couple there, if that would help the Committee.

DR. BLALOCK: Okay. And I think that brings us to the end of the questions, so let's go ahead and take the break. And I'm looking at my watch. It looks like a -- let's resume at 3:50. And I'd just remind the Committee members again not to speak about the topics that we're discussing during the break. So we'll resume at 3:50.

(Off the record at 3:31 p.m.)

(On the record at 3:50 p.m.)

DR. BLALOCK: I'd like to call the meeting back to order.

(Pause.)

DR. BLALOCK: And, Ms. Duckhorn, would you like to review the charge to the Committee now?

MS. DUCKHORN: The moment you've all been waiting for?

Thank you, Dr. Blalock, members of the Committee, and guest speakers. We've heard a lot of interesting presentations framing the issue, and you've asked a lot of great questions.

This meeting is to obtain your advice on how information in labeling under the Pregnancy and Lactation Rule is being perceived and used by healthcare providers and other stakeholders, factors that are critical to healthcare providers' interpretation of the data and counseling of pregnant women on the risks and benefits of medication, and how to convey risk information to healthcare providers to accurately and adequately inform risk-benefit considerations for medication use during pregnancy.

We ask that you respond to a series of discussion questions located in your packets and as separate handouts. For your convenience, we will project the questions as you move through them.

Question 1. First, discuss how the factors below impact healthcare provider decision making and patient counseling, in terms of risk perception, interpretation of uncertainties and available data on drug use in pregnant women, context of drug-associated risks in relation to the background risk

information on major birth defects and miscarriage, benefit-risk considerations, and medicolegal considerations.

Do you want me to read all of them, or just go --

DR. BLALOCK: So open it up for discussion.

MS. DUCKHORN: Sure. Or do you want me to read all four?

DR. BLALOCK: I'm sorry.

MS. DUCKHORN: Let's move to the second question. I'll just --

DR. BLALOCK: Okay.

MS. DUCKHORN: -- go through them. Okay.

2. Discuss how effective PLLR has been in conveying safety evidence in pregnancy that is useful to benefit-risk decision making. Include in your discussion the following:

- Interpretability of safety evidence in drug labeling;
- Interpretability and impact of animal data on decision making when there are no human data;
- Information that has been unhelpful or has led to unintended adverse consequences (for example, avoidance of needed treatment).

And if appropriate, recommend strategies to improve risk communication that comply with PLLR requirements.

2B. Consider the following situations and discuss best practices to communicate the following in drug product labeling, if appropriate:

- Observational study data where inconsistent study findings preclude a clear conclusion;
- Observational study data where the weight of evidence show no increased risk for major malformations, but some data suggest an increased risk;
- Observational study data where there are methodologic limitations (for example, when to include or not to include these data);
- When there are no study data, but cases reported in the pharmacovigilance safety database are available.

3A. Discuss your interpretation of the following phrases currently used in the PLLR Risk Summary, and provide any suggestions for improvement, if applicable: "adverse developmental outcome," "limited data", "available data are not sufficient to inform the risk," "available data have not reported a clear association."

3B. Discuss how language affects the following:

- Physician willingness to treat pregnant patients;
- Patient decision making and adherence to treatment;
- Pregnancy planning and prevention (for example, need for pregnancy testing before prescribing a medicine).

3C. Discuss intended and unintended consequences, including prescriber liability, that may occur with certain

language or communication approaches.

4A. Suppose FDA has some evidence of a potential drug safety issue for pregnant women, but the evidence is limited and preliminary. What should FDA consider in deciding when and how much to communicate to the public about what it does and doesn't know? And what should FDA consider in deciding whether to wait?

4B. Suppose FDA has determined that communication about the potential for adverse effects in pregnancy is necessary. What additional comments do you have about how FDA can communicate to maintain a balanced assessment of the benefit and risk and to minimize unintended adverse consequences?

DR. BLALOCK: Okay. So now you wanted to open it up for discussion. Or there was some talk before the break of providing a medication guide. Was there a decision on that? And I think something else as well.

DR. YAO: We're happy to do that if the Committee would like to see some examples. We're ready to provide those. So I have my colleague, Dr. Tamara Johnson over there, working with our audiovisual expert.

So the first thing we were going to present was the Section 17, patient counseling information. As we're projecting, I do want to make sure it's very clear to the Committee that all we did, for purposes of just clarifying and providing examples, pull up something that we knew was an

example. This is not intended to be singling out this product in any way. And so I want to make sure that the Committee is very clear about that.

So this is Thalomid, which we thought would be a fairly straightforward example of a product, a thalidomide, where you can see this is the information that we generally include in Section 17, patient counseling information. And you can -- sorry, patient counseling information is here.

So as we had described, patient counseling information is the last section in standard prescription product labeling, and it's intended to give a prescriber or someone who's having a conversation with the patient some important information about serious warnings and precautions, and also to counsel about any programs that would be available that are needed to gain access to the product. And in this case, Thalomid is only available through a REMS program, and that's Risk Evaluation and -- REMS is Risk Evaluation and Mitigation Strategy, right.

So this is the patient counseling information. And then if we scroll down, I think we have the beginning -- yeah, we close out the -- this is the medication guide. So this is written in language that is again, bulleted, single concepts, and in language that is intended for the patient.

Are there any questions or comments about this?

DR. BLALOCK: Dr. Lee has a question.

DR. YAO: Sorry.

DR. BLALOCK: Dr. Howlett. And your microphone.

DR. HOWLETT: Okay. Point of clarification: What percent of the drugs that you're dealing with are this clear cut? It seemed like, you know, all the examples that we were looking at was like, oh, maybe this, maybe that, who knows. And this is like, you know, this is clear.

DR. YAO: So you -- if I could respond. This is Lynne Yao.

So we didn't present these in your briefing document because we kind of do feel like we know how to label something when we have clear information. This was really to provide you a little bit of additional context to, you know, show you when we know something and how we describe it versus when we're less sure. And I would say that the universe of products like this is extremely small.

DR. BLALOCK: Dr. Lee.

DR. LEE: Okay. So I'm thinking back to Dr. Kreps's question and Dr. Wolf's question from before about the uncertainty of the data and the response you just gave.

So I think of medicines as like four buckets. The first is it's safe for the pregnant woman; it's unsafe for the pregnant woman; risk is known and that's balanced with other factors; and then there's risk is unknown.

So of the percentage that you describe, I'm expecting that Questions 2 and 3 relate to bucket 4. Is that correct? Is

that what you're asking us, to message things that have unknown risk or uncertainty?

DR. YAO: Generally speaking, yes. When the data are limited or there is conflicting information or that we don't have a clear --

DR. LEE: And what percentage of medications fall into that category?

DR. YAO: The majority.

DR. NGUYEN: So -- yeah.

DR. YAO: The large majority.

DR. NGUYEN: I would clarify that something this clear, thank goodness, is pretty uncommon, when the risk is undeniable. Conversely, it's also rare for us to say that the drug is perfectly safe in pregnancy. And where you see that, really, are more of the products that are approved to treat a pregnancy-related condition because the safety data have been adequately generated for those specific products.

For the most other products, which is the vast majority, is going to be in the nebulous two buckets that you described.

DR. LEE: Yeah. And I think that's one of the challenges that prescribers have is that your uncertainty is coming down to the prescriber, and we don't know what to do. And I think that's the challenge that we're seeing based on what you guys are trying to convey.

DR. NGUYEN: We completely agree. I mean, I think it's a

two-phase situation. One, we have to label the information that we have now, and we know that information is far from perfect so we're discussing how best to do it, how best to do in the way that's the least confusing and hopefully useable. And then certainly we -- at a federal level, we have discussions of how can we stimulate research in pregnant women so we actually can get the information that's needed.

DR. BLALOCK: Let me ask you all just one question. You're going to -- you know, you came back and showed us the medication guide. Was there another document that you wanted to show us as well?

DR. YAO: Sure. The last one is --

DR. BLALOCK: Let's look at that before I take more questions.

DR. YAO: Okay. The last one is an example of PLLR product labeling in which we have a clear risk based on human data. I did include that sometimes we'll label it based on animal data too, but in this particular circumstance -- again, as just an example. We are not here to discuss this particular product in any way.

But as an example of how we have communicated the information when we have human data that describe a clear risk during pregnancy, the example is here. So this is Section 8.1, which actually describes a pregnancy registry too, but the risk summary is what I would direct you to.

There's also information as it refers you back to -- actually you're not supposed to refer back up, but it talks about clinical considerations. And if you go up to warnings and precautions and the boxed warning, it's all in there.

So can we scroll up to boxed warning as well?

So there's the box, embryo/fetal toxicity. And then it's also described in a little bit more detail in warnings and precautions, Section 5.3. And we can go there, and that's where it's listed, in terms of the risk that we've identified, in terms of human clinical data, and then again in the risk summary, and then the human data sections of 8.1.

DR. BLALOCK: And let me just clarify. This is the professional package insert?

DR. YAO: Yes.

DR. BLALOCK: Okay.

DR. YAO: This is -- and this is an example, just an example of PLLR converted labeling that includes -- again, when we've been clear, we've felt like we were clear that we knew that there was a clear risk, based on human data, this is how it has appeared.

DR. BLALOCK: And, you know, and in the materials that we were sent prior to the meeting, I think that there were actually, at the back of those, eight different examples of this.

So Dr. Wolf.

DR. WOLF: I mean, I guess just a couple of comments because I think I'm getting my -- I've totally understood my issue now with the counseling piece, that it still comes back to what do you want to accomplish in terms of the outcome? And I get it, getting rid of the ambiguity and the uncertainty, which we deal with a lot, in terms of how do you communicate uncertainty to the patient, but you're actually saying that this may stop short because it may never get to the patient.

But the odd thing here is the default seems to be, from the data this morning, is that people, that prescribers are not using products when they could be potentially used but it's still kind of unknown. So this is -- I mean, I'm a little bit kind of now in the ditch with you and understanding the full appreciation of the problem.

I guess one comment would be also is do we know the difference between -- you know, there's all this information coming out, especially with new medications, where there may be more unknowns where especially a lot of these products, especially when we were talking about SSRIs earlier, may be more commonly used in primary care, which is the work that I mostly focus in on, where there is more reticence to not want to -- you know, the default, well, if there's any issue, even if it's ambiguity, I'm just not going to do it.

Has that been something that's kind of been clarified? I mean, it doesn't change how you message it, other than the fact

that this is a lot of content that will definitely not -- I mean, they'll stop short of the black box in terms of trying to figure out whether or not they're going to learn more about how they might potentially use it.

DR. YAO: Lynne. Yeah, so let me just clarify again.

Our goal is, as you've read -- heard the questions and we've provided just a couple of examples to sort of say this when we've been more certain. The examples that Dr. Sahin presented earlier are examples when we've been less certain.

We need help in understanding whether the statements that we have used, and that's part of the first couple of questions, does that -- are those statements helpful? How are they not helpful? How do they -- do they persuade you? If you are unlikely to prescribe, to not prescribe, are you swayed to prescribe if you were not going to -- again, we want some information and feedback from you about how these statements may be helpful or unhelpful.

DR. WOLF: And if I could just follow -- because I think this is really helpful so we don't spend not only the rest of today but tomorrow providing you feedback on things that you already know, and as the titan -- this is a very narrow ask. Am I interpreting it correct, in terms of what you want the RCAC and other members today talking about?

It's really about the messaging and only the messaging specific to the prescriber and not a lot of the ancillary

stuff. You don't want us talking about more data and all these other issues. You want us at the ground, okay.

DR. BLALOCK: Dr. Nahum.

DR. NAHUM: Yes. Thank you. Dr. Nahum.

You know, just listening today, I just want to -- I have two questions for FDA. But it sounds like this is not so much a communication deficit, per se, as it is a knowledge deficit. It's very difficult to communicate well when you don't know what it is you're trying to communicate.

And so I think that's part of what is going on in terms of some of these questions. Dr. Lyerly asked a question before as have several others that I did not really hear an answer to. And this revolves around the question, really, of what a minimally clinically important difference should be considered with regard to risk for teratogenicity.

I know that FDA had previously set a threshold with registries, for instance, of a relative risk or an odds ratio of 2, 2.0. And this was there for a while. It got kind of rolled back. But that, at least, would put a stake in the sand, if you could give us a number like that.

And what this gets back to, really, is the idea of powering. And when we run clinical trials, you know, for primary approvals, to demonstrate safety and efficacy, we always have to power these trials. And we're not sure what the result is until we get either to the end of the trial or a

certain number of events or something like that.

That's not what you're telling us here. That's not what I'm hearing. There's sort of an undercurrent here of a rolling assessment of incoming data, as it comes in, and that we should update information in labeling and communications based on that, even if the difference is not clinically important, or if it's not statistically significant in a robust sense.

So I guess what I'm asking you here is can you give us some guidance as to what you would consider to be a clinically relevant change in the acquisition of new information and its processing, so we know when to communicate things, what to communicate, and when to update labeling?

DR. YAO: Lynne Yao.

So I think that's a very fair question. And I think it's a very fair point, but that's not the point of this Advisory Committee, I'm sorry to say.

We really -- and you're right, we've published in guidance that says, you know, we want to power a prospectively -- prospective pregnancy registry to identify a relative risk of 2 or greater, and you may look at the labelings and the pregnancy registries we have open on our FDA website and know that these registries have been running for years and years and years.

So that's a whole separate issue about what data qualifies as sufficient to change labeling. And that's a conversation that we have with given, you know, companies on a daily basis.

But when we've decided that there's information that should be included in labeling, are we communicating in that way that describes the uncertainties, the information that we have? That's really at the heart of what we'd like to have the Committee describe or give us advice on, partly because we're 500 labelings into this, and we don't know if we're doing what we have been told we should be doing under the intent and spirit of the rule, of the PLLR.

DR. NGUYEN: And --

DR. YAO: I would be -- sorry. I just would be interested to make sure I am accurately reflecting others' position at FDA.

DR. NGUYEN: Yes. So I would just add the clarification that we're in a position now that we have to put available data in labeling. It's the good, bad, and ugly. We're not tasked with only putting in information that's going to change practice. It may do that, but the vast majority of the time, we have to put in what we have, and we're trying to do it in the way that hopefully best serves the public, and so that's where we need feedback from you.

DR. BLALOCK: Dr. Spong, it seems like you want to react to something that was said.

DR. SPONG: Right. So this is Cathy Spong. And I think I just want to provide, if I may, since we're in the discussion period, for the Panel members who don't deal with this on a

daily basis, that in pregnancy, we don't have the randomized trials on the majority of medications that people are taking.

These medications are put through randomized trials, but they are not in general inclusive of pregnant women. And oftentimes when a woman becomes pregnant, she is then removed from the trial, and we do not get that outcome information from that patient.

So yet, if you can believe it, there's a lot of women who get pregnant in this country and around the world, and many of those women are taking medications, and they continue to take those medications when they are lactating. And yet that developing fetus and that developing neonate and all of the exposures that they can have, we don't have information to provide those women and their families on how best to give those medications.

I think it's important to understand, and I really appreciate the clear presentation this morning, that medications that are approved for use in adults, it's not that they are off label in pregnancy. They're still approved. If that -- if the reason that they're on that medication is still happening in pregnancy, right, so they still have asthma or they still have hypertension, they're on-label use of that medication. Yet how do we counsel that woman about what the impact is for the fetus and for the neonate?

If we think there's a dearth of information in obstetrics,

and there is, there's even more of a dearth of information in lactation. Yet we have to provide that information. And we, as providers, have to counsel these women and their families.

And I think what we're being asked today is to say, is this PLLR, in its new revised state, providing the information that you want to be able to get across to these people? Yeah, the data's not good. We're not going to change that today. We're trying to change it; we're trying to do what we can. But how do we get the information across given that we have to put it in there? So if there is some animal data, we've got to put it in there. How do we make it understandable that it is or is not translatable to humans?

And I think, just going back to Dr. Lee's question earlier, you know, is it safe, is it efficacious? We don't know about that in pregnancy, to be perfectly honest. And what is safety? Right. Is safety not a malformation? Is safety not ADHD? Is safety not being retained in kindergarten? Is safety not going to a public university? I don't know what safety is. But it's really difficult in pregnancy to ever say something is truly safe.

DR. BLALOCK: I've got five more questions here, and then, you know, when I got through these, then I really do want to get to the questions and start us to focus the discussion of the questions that the FDA wanted to have answered.

So let me just say, the folks I've got are Goldman, Baur,

Tracy, Slovic, and Pleasant.

So Dr. Goldman.

DR. GOLDMAN: Could -- this is Myla Goldman.

I guess -- I have a question depending on your answer to this, but to clarify, the counseling piece, which is different from the patient information, the physician counseling piece, is that encompassed in what we're looking at? Is that considered part of the package insert?

And is pregnancy always a component of the counseling piece, or is it only present or absent depending on what's known about that particular agent? Could you clarify that?

DR. YAO: So it is under discussion, but in the -- as I think Dr. Wolf has articulated, and Dr. Spong, thank you both for, you know, speaking very clearly what I don't think I was able to do. But in those situations in which there is really uncertainty and different levels of uncertainty, we still have to, and we're required by the rule to, provide that information, communicate that information.

That's less likely -- in those situations, it's less likely we're going to have something in patient counseling.

DR. GOLDMAN: So I think --

DR. YAO: So it's -- so --

DR. GOLDMAN: Yeah. So then I have a comment, I guess. Is this -- okay. So it seems to me, in summary, sort of from the day, that there is sort of two -- I mean, there's really

three end-users, but two end-users. One is the provider, who is trying to make the best decision at that moment about that individual patient, but then sort of the second, secondary end-user that has been identified are these women who are living with chronic disease, who are making forced decisions between their illness and potentially the health of their baby.

And so to me, if it's not part of the PLLR, it seems obligatory to protect against that second end-user, that the patient counseling segment needs to always be inclusive, and particularly when information is not known, to emphasize on the risk of the disease itself.

And this gets back to a point that I think was made by our patient representative advocate about that we can't separate these two. And I understand the language, right, that so we can't have patient language in the physician insert, but we could use the physician counseling segment as a way to protect that second end-user, which is protect women living with chronic disease from these forced choices off of drug, when we know that the disease itself is devastating to them, as in the case that I sort of navigate every day.

DR. NGUYEN: Hi. Christine Nguyen.

So I think I just want to tease apart Section 17, called patient counseling, from the general concept of patient counseling.

DR. YAO: There's specific language, right?

DR. NGUYEN: There's specific criteria. And as Dr. Yao mentioned before, usually the elements that would drive a certain piece of information to go into patient counseling has to do with warnings, precautions, pregnancy testing, or any other specific testing before you're supposed to take the drug, adjustment in dose, those type of information.

As far as what you're describing, in terms of pulling out and translating the available data in pregnancy and then counseling that with the risk of an untreated illness, that information is contained in Section 8. And so that's why we keep going back to this section.

If we have information on pregnancy that does not provide a clear risk in pregnancy, it's the elusive language that you saw this morning, that will not be pulled into Section 17, the patient counseling. Again, as I mentioned, the purpose of Section 17 counseling is very specific to those elements that I described, adjustment in dose, special warnings, precautions.

So, I mean, part of that has to be -- it's a little bit of FDA educating the public, what information lays where in labeling and how to use it.

DR. GOLDMAN: I guess I --

DR. BLALOCK: I think we --

DR. GOLDMAN: Yeah, okay. Perfect.

DR. BLALOCK: -- keep moving.

Dr. Baur.

DR. BAUR: So Cynthia Baur.

So, Dr. Blalock, I have just a procedural question for you. Given that we have these three blocks of discussion, and I'm sure that all of us have lots of advice that we want to offer, will we be -- will the discussion be structured around those four questions then, or how do you envision that?

DR. BLALOCK: Absolutely. And, in fact, you know, I'm probably trying to push people a little bit to end this discussion right now so that we can get to the questions which the FDA has prepared and would like to have us respond to.

So what we'll go do is go through each question individually.

DR. BAUR: Okay.

DR. BLALOCK: And I do intend to end pretty promptly at 5.

DR. BAUR: Okay.

DR. BLALOCK: You know, even if it's in mid-sentence.

(Laughter.)

DR. BAUR: So I do have a question for the FDA but not about the things people have been talking about.

DR. BLALOCK: Okay.

DR. BAUR: I wondered if the FDA staff had decided if, because this is public information, if the federal Plain Writing Act applies to this, because if it does, then that provides certain guidance already in terms of the way that you would approach providing this information to clinicians. So

has anyone done that determination yet?

MS. DUCKHORN: Hi, Cynthia. As you know, plain writing means it's written for its intended audience. In this case, I mean, the labels are written for the intended audience of prescribers. But these labels do not go through any kind of testing, or they don't use the Clear Communication Index, for example.

DR. BAUR: Right. No, I was thinking more some of the techniques around, you know, the way information is organized, making sure that you have a main message, those kinds of things, even if you don't -- so just in full disclosure, I have a tool, when I was at CDC, called the Clear Communication Index, and that's what Jodi's referencing.

But also, just in terms of the Federal Plain Language Guidelines, that's a set of guidelines that all federal agencies are supposed to use when providing public information. So there's kind of a foundational set of principles that might guide that. So I just wondered if that determination had been made. That would provide some direction already in terms of kind of simplifying and structuring some of this information.

DR. BLALOCK: Thank you.

Dr. Tracy.

DR. TRACY: I actually have a question about the questions, so I'll wait.

DR. BLALOCK: Dr. Slovic.

DR. SLOVIC: Right. So we have the science that underlies the development of medicines. It's very elaborate, expensive; it takes a lot of time and effort and money. And sometimes it's not definitive, particularly in this case with pregnancy, where sometimes you can't do the studies that you would like to be able to do to get better data.

So you have all of that, and this provides information, as I understand it here, that is going to go to providers. And the question, since this is a meeting on communication, is, you know, how adequate is this information? How, you know, how could it be improved?

There's a lot of questions that have been put forth. And I don't know that we know the answers to those questions. Now, we can sit around the table, and we can all speculate on those questions. But there's another way to answer those questions, and it's a lot easier than the science of developing the information to design the drugs and so forth.

It's the science of risk communication. The fundamental tenet is test your messages. It's very easy; it is far easier to take various communications and then try them out on representatives of your audience and see how they react to that. Ask them questions, get their, you know, open-ended -- you can do this. It's very, very easy, and you always learn.

What you learn in the area of risk is that risk is complex, that people respond and interpret it in ways that you

might not have expected them to do it, even professionals. We use -- risk is very difficult to understand, and so we have all kinds of mechanisms to try to simplify it. I mean, that's why we go to the ABC kind of thing is because, you know, it's a way of simplification, something that's complex.

So is it within FDA's purview to do research or to sponsor research to try to answer some of the questions you're asking of us?

MS. DUCKHORN: They may not like this answer. This is Jodi Duckhorn.

We do have the ability to do testing, to do cognitive testing. And unfortunately for -- most of the time, the time that it takes to do testing is not built into the timelines that are allowed under the user fee authorizations. And so they're already in very tight timelines, and there's just not a lot of time built in for testing.

If after the fact, after a drug is approved or on the market and the label is out there, if one of the reviewing divisions came to my staff and asked us to do cognitive testing, we could do that. And it just opens a new timeline for a lot of back and forth with the sponsor and the division.

DR. SLOVIC: So let me just speculate. My guess is that if you were to do testing on things other than something like thalidomide, where you've got these inconsistent results or lack of human data, animal data that is complex and

inconsistent, you'd find that the communication is a mess, that it wouldn't be effective. People would interpret the message very differently from one person to the next. They wouldn't find it helpful for decision making. That's just a speculation, but it could be tested.

DR. BLALOCK: And I think, Dr. Slovic, that, you know, a lot of people in this room would, you know, would agree. And, you know, I think that some of the questions that we'll be addressing really will, you know, sort of invite that as a recommendation. So I think that that will come -- you know, the user testing as a recommendation from this meeting. I'll be surprised if it does not.

But let me -- Dr. Pleasant has a question. Oh, he's passing. I'm going to, so call this portion to an end then. And if I can get pulled up the first question.

So there are four questions that our charge is to discuss. And part of my job up here is, towards the end when we get done discussing, is to try to summarize. And so, you know, I know that it's hard to, you know, sort of stay focused on the questions, but as much as we can do that and compartmentalize and really focus on the questions makes my job easier.

And do we -- are we going to get -- there's the first question. So I'm going to -- actually, Dr. Cappella had a hand up earlier.

So the first question, discuss how the factors below

impact healthcare provider decision making and patient counseling. And you can read the factors here yourself.

Dr. Cappella, did you have a comment in response to that question?

DR. CAPPELLA: I can find a way of turning my comment into an answer to this question.

DR. BLALOCK: Oh, since I kind of put you on the spot, I'll let you.

DR. CAPPELLA: That's okay. No. I would focus on Subpoint B here. There is -- and this is in, partially in response to Paul's observations as well, and that is that we -- while we don't have data about presenting information -- informational uncertainty with regard to the particular drugs we're talking about in pregnant women, we do have a lot of evidence that suggests that in the press, broadly, when there is conflicting information about diet, about behavioral actions that are healthy versus unhealthy, the role of red wine, white wine, whole grains, not whole grains, and so on and so on, when there is controversy within the public information environment, part of what we know is that this increases people's uncertainty and frustration and cynicism about those particular products and also about the science behind them.

And so part of what I think is of great concern here, and I think this is part of what Paul is referring to, is the notion that the presentation of information in terms of the

degree of uncertainty that is available from the prevailing science will undermine the way in which people view that science and probably undermine, to some extent, the credibility of the communication about that science.

That concerns me a great deal. And I think that, you know, how that is communicated and the way in which that can be framed so that it somehow mitigates the cynical response that might result is a real challenge. And I don't have any ready answers to that, but I think that that -- I take that to be the challenge that you're putting before us.

DR. BLALOCK: And, Dr. Slovic, since you were referenced in that comment, let me turn the microphone to you for a minute.

DR. SLOVIC: Well, I agree with that comment, but I wanted to address the risk perception, first point there, or more broadly the concept of risk, which we use all the time, and refer you to Elizabeth Conover's very excellent presentation this morning of all of these factors that influence how we judge probability.

But I think 90% of her talk addressed risk as a probability. And she even said, well, maybe it's better to use chances rather than risk. And I think one of the problems in thinking about communicating about risk is that risk has multiple definitions, of which probability is one.

So there's at least -- there's more than four, but the

four that are, in my mind, most prominent and illustrate the problem of communication, the first is risk, we use risk when we mean a hazard. Something's dangerous. You know, like airplanes are a risk. It's a hazardous thing.

A second definition is risk as a probability, you know, what's the risk of some consequence. We're implying what's the probability?

A third definition is risk as a consequence. So what is the risk of getting, of letting your parking meter expire? The answer is getting a ticket. That's a consequence.

And the fourth definition, I think, is perhaps the most defensible, if you want to talk about risk, which is, risk is some combination of the likelihood of something going bad and the severity of the consequences. What's the risk of riding a motorcycle? What's the likelihood of different kinds of accidents and the severity?

And I think if we talk about risk and we really mean probability, we should say probability, and it's very -- you know, there's a lot known about how to communicate probabilities.

And the problem -- but one of the problems with using probability as your definition of risk is it leaves out the severity of the consequences. So a well-known risk perception researcher did a study of a whole bunch of different consequences and asked for the judgments of risk.

And some of these were pretty serious, but what came to the top, the item that was judged riskiest of all these things was getting the wrong change in the grocery store because it was more likely than some of the other things, like getting AIDS. Okay, getting AIDS is less likely, so people judge it as risky.

So we have to also consider consequences in risk. So that's just the beginning of thinking about communication. And it gets more complicated from there, but I'll stop here.

DR. BLALOCK: Let me ask you a follow-up question, though. You know, in the context of healthcare provider decision making and patient counseling, you know, how would you make that link? What are the implications, do you think, of what you, you know, just were describing in relation to healthcare provider decision making and patient counseling? Do you use certain words rather than others?

DR. SLOVIC: Again --

DR. BLALOCK: Just as an example.

DR. SLOVIC: Again, I think you have to test your messages. The problem is that even -- we talked about having clear information. Even if you have clear information about probabilities, then you have the question, well, how do you express the probabilities with some -- Conover presentation. Or in the book that you referred to that Baruch Fischhoff edited, I'm sure it's in there.

So, for example, if something -- if you say -- even if you have good data and you say, well, if you take this drug, you have a -- 1 in 100 pregnant women will get this certain consequence. Okay. That's 1% or it's a 0.01 probability or it's 1 in 100.

Each of those framings will lead to a different response. If I want that person to be more concerned, I'll say 1 in 100, because we know that that -- people image the numerator. They think -- they have an -- they think, well, maybe I could be the one. And that scares them. And that feeling then becomes a representation of risk.

If you said that the probability is 1%, that's a small number. It doesn't create that image. So then, so which way should you present it? Both ways, one way? And that's where we have clear data.

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thanks. I think that, you know, going specifically to this question, all of these clearly impact how providers, and I'll call myself a provider for this question, give that decision making and that counseling. And I think, going back to this question of 1 in 100 or 1%, or you could say 99 out of 100 will not, right.

And oftentimes when I'm talking to a patient, I'll say, you know, your risk is this, whatever 1 in whatever it is, and I'll say, you know, I've got patients where it's 1 in 5 versus

1 in 10,000, and they may make very different decisions because it's based on what your perception of that risk is.

And I think it was really important, as was brought up earlier this morning, that patients and people need to realize that they're taking risks every day. And just because they're making a risk decision on this medication, they're making -- and yet they were willing to get on the D.C. highways and come and see me in my office and not even think about the potential risk that they were having there, right.

So it's risk out of context. Everything we do involves risk. And so to have that communication with the patients to explain to them, this is just one of many, many different things.

But the risk itself isn't the only thing. You know, if we don't have for them to tell them whether or not the studies are strong studies or are weak studies, if in fact, that's not clearly laid out to the provider, then they may be giving information that isn't helpful to that patient.

So knowing how -- what those studies are and how strong they are is incredibly important. Knowing what the background-related risk is something that I think is really, really important for the patient to understand that, no matter what, pregnancy is risky, lactation is risky, and you've got to understand what those risks are.

And then, of course, the benefit and risk considerations

to understand, is it better for you to take the medication or not to take the medication? Is it better for you to provide nutrition via nursing and lactation versus not to do that, and what are the risks of not lactating, for example, right. And that's not commonly -- it's certainly not included in the labeling, but it's something that you've got to convey with that patient.

And then medicolegal considerations and this risk of liability, both for the provider and for the patient, are both really, really important. So all of these aspects factor into the decision making of a healthcare provider.

DR. BLALOCK: And just let me interject a comment sort of in relation to this. You know, I think that some of the information that is provided in the new labeling, like risk-benefit, what is the, you know, risk among diabetes patients? And we've heard a lot about mental health issues. What are the risks if you don't take the therapy?

And I actually think a good thing about the new labeling is at least there's an interest in trying to get some of that information in there about, you know, those risks.

And the other thing that is new in the labeling is providing information about the, you know, risk of abnormalities as well as, you know, miscarriages, you know, the baseline risk among people who are not taking the medication. And I think both of those changes in the labeling are trying to

address, you know, B and C, at least the way that I interpreted it.

So the next person on my list is Dr. Pleasant.

DR. PLEASANT: Thank you.

I'm not disagreeing with anything anybody said. Still, these factors clearly all impact healthcare provider decision making, which in itself isn't a complete statement because the decision should involve the human being that's also in the room other than the healthcare provider. But it, for example, doesn't include economics. Just quickly, it doesn't include culture.

Now, I guess you could say that you've subsumed culture into risk perception, but I'd hate for that to actually be the case because it deserves highlighting.

We can plain language the language that you're using around the uncertainty all day long and come up with some really lovely plain-language solutions, but plain language does not guarantee an informed decision.

So part of the communication, as much as you might not like this, so be it, has to include a process. We know how to help people make informed decisions in the face of uncertainty, but that's a process, not an explanation of the uncertainty.

So I would suggest that you be open to including that science of the process of making an informed decision in the face of uncertainty as part of the communication to healthcare

providers, to help that decision-making process in the room between the doctor and the person. I'm personally trying to ban the word patient, by the way, because who said you needed to be patient to receive medical care?

Right. So there's a process there that we could talk about and extrapolate quite a bit in addition to the plain language of the uncertainty problem, how to explain the lack of scientific data, which would probably actually -- I think that would help you reach the ultimate goals that you're trying to reach, because in a pithy way, remember, when there's a doctor and another person in the room, there are two people with problems.

DR. BLALOCK: Dr. Berube.

DR. BERUBE: A few things. First of all, I think one of the answers to A is D. I mean, there's an order effect, which we did a study on sunscreens, melanoma, and certain types of ointments for Australia. And we discovered that if you talked about the benefits before you talked about the risks, the impacts were completely different, you know, with the audience.

And we just did a study in Singapore and the United States on Chikungunya and on Zika viruses and vaccines, and the same thing happened, right, where if you start with the benefit factor before you go into the negative risk factor, what ends up happening is, it re-contextualizes it.

It's almost like an anchor of a sort. You know, you're

giving them the positive message, and then when they take the positive message and try to calculate the negative, they start from where you started. Right. So they're starting at that post and then working downward, which is always good for you.

I think the real challenge you have with this issue is it'd be really nice if we can give you a confidence level to each one of the approaches you're taking that would tell you how the physician would interpret your message, but like as Paul mentioned, the ideal way of doing this is with testing more than anything else.

There is a strange source that I'll give you. There's a professor of mathematics at Temple named Paulos who wrote about innumeracy. And on page 127 of his book, he talks about logarithmic safety indexes. And instead of doing the A, B, C, X thing, he did a system like you would use for seismic activity and towards indicating what type of, you know, of earthquake you would get. And it's much more granular.

And when it's been tested, it sort of reduces the exaggeration, hyperbole, people introduce into risk estimations, because the granularity of it gives you much more choices. Maybe that's something your physicians might like. But if you're interested, Paulos's book is everywhere. It's called *Innumeracy*, and it's a pretty good book.

But I agree the last thing was just contextualize all this. You know, I spent years and years and years talking

about the risk of nanoproducts, the last 20 years collecting data on this stuff, finally did a study which contextualized it with the public. We found out the public thought on a list of 25 issues, it was 24. Right.

We sort of stepped back and went wait a minute. We had to completely reexamine all the research we had done for years, because if you look at it within context, it's really unimportant.

And when you start in talking about all the variables that go into a decision when a woman decides to have a child, I think you're talking about a rich set of variables here that can work quite effectively in contextualizing even the worst risk, even the risk that would be on our REMS drugs.

But it has to start with people who have your problem, whatever it happens to be, need to be medicated. And those who are medicated benefit in this way. Is there a drawback? Yes, there's a drawback, but if 100 women did what I'm advising, 97 of them would have healthy children. And it's really important to do this. And we found it in vaccines, with Chikungunya and Zika.

DR. BLALOCK: And I just want to make sure that I understand. So you're saying that folks are more likely to accept a risk if you start by describing the benefits and then going into the risk in terms of the order? Is that what your data suggest?

DR. BERUBE: It's a little bit acceptance, but it's a lot of understanding.

DR. BLALOCK: Understanding.

DR. BERUBE: They're much better to understand the risk --

DR. BLALOCK: Understand.

DR. BERUBE: -- when they put it -- you start with the positive implications rather than the negative. Rischiare is Italian for circumnavigating cliffs. Right. It's not about falling into the cliff; it's about circumnavigating it. And we seem to have lost that.

DR. BLALOCK: Okay. Thank you.

Dr. Goldman.

DR. GOLDMAN: My comment relates to I guess E, medicolegal considerations, and I'm just thinking about this through the lens of what I do, which is, you know, as a neurologist, so not someone that's committed to necessarily initially thinking about caring about pregnant women, right, went into neurology, but then take care of this disease, this population where they're living with a disease during their childbearing years. And we've seen -- I see tremendous variability on what patients are advised about what to do.

And in the absence of their drug, they're at risk for having a neurologic event that then completely handicaps their ability to care for the child that they now have. So the stakes are also really high.

And what I've sort of distilled down in thinking about this today is in addition to thinking about risk and risk tolerance and the risk tolerance of patients and how do we, you know, put the language, but it's actually the liability. Who's shouldering the risk?

So if a physician gives a medication, that physician is shouldering all of the liability. If the physician withholds a medication, the patient is now shouldering all of the liability of the disease. And so the medicolegal implication here cannot be ignored.

And so I think that -- and then you add in the fact that there's no time. So if I have 5 minutes to meet with a woman who wants a drug that has a unknown or uncertain risk, I'm just going to tell her no, you can't have that and be pregnant; that's not good for you. And now I have alleviated all of my liability, and she walks out carrying the entirety of the risk now.

So it's not just about risk perception, but it's about who's shouldering the liability of any given risk. And I think that has to be part of how we think about this in coming back to importantly -- well, I guess that's all I'll say about this portion.

DR. BLALOCK: Dr. Lyerly.

DR. LYERLY: So I have something to say, but I just wanted to build on that first. I think part of it is liability, but I

also think it's responsibility. So whether or not there's a risk of being sued, I think what we're really talking about is who is ultimately responsible for the harm that would ensue from the decision, right.

And so -- right. So I think patients look to their doctors to partner with them in some way so that they can share that responsibility. Providers, I think, are looking maybe to the FDA to share that responsibility. And so I think, I just think broadening that discussion to the notion of responsibility and getting beyond these medicolegal considerations and really think what's morally at stake for people.

DR. GOLDMAN: This is Myla Goldman.

And this is an opportunity to help share that responsibility from the FDA physician arrow.

DR. LYERLY: Yeah.

DR. GOLDMAN: Right, I think is key.

DR. LYERLY: Right, right, right. So that was my thought just on that comment, but I also wanted to make a comment about this list and just remind us that part of what is particularly difficult here is the fact of pregnancy. So it's not that we just have problems with risk perceptions or just have issues with risk-benefit considerations, but that pregnancy makes all of this stuff particularly difficult and in certain -- and in many ways.

And one is that people do not like risk in pregnancy, at all. And many years ago, like 25 years ago, a legal scholar, Vanessa Merton, talked about this quixotic quest for zero risk to the fetus, which is part of the reason that we don't have any data in the first place, right. Nobody wants to impose uncertainty or risk on pregnant women or fetuses. So the researchers don't do it, so they shove it into the clinical setting.

Another problem people have with risk in pregnancy is that they notice the risks of intervention, but they don't notice the risks of nonintervention. And I know that anybody who's practiced around the room has been in a position where they are trying to convince other providers who are not as used to taking care of pregnant women that something is needed, an x-ray, a medication, you know, an antiplatelet drug, whatever it is, and that really ultimately, in the long run, this is going to be best for the woman and her fetus, but it's hard to get that intervention in place.

A third is that people are very uncomfortable with the idea of trading off risks and benefits between really the two entities that we're talking about. I hate to call pregnant women an entity, but it's true. So here we have two entities that these interventions will accrue certain risks and certain benefits to one or the other, and they're going to be different for those two. And there's a deep discomfort with making those

kinds of tradeoffs, and there isn't an agreed-upon way to do it.

And so all of the data that's in the label is being provided against a backdrop in which people are very uncomfortable with and have distortions in reasoning about risks in the context of pregnancy.

So I don't know exactly what to do about that, but I think it's important to keep it in mind as we think about, you know, what we're doing here and how best to do it. That's it.

DR. BLALOCK: Dr. Baur.

DR. BAUR: So -- this is Cynthia Baur.

So I actually see A through E very linked, based on what we heard this morning. I think we got two answers about what clinicians or prescribers, I guess to use your word, what prescribers are doing. They're either defaulting to not doing anything, right, to reduce the risk as much as possible to zero, or they're giving conflicting information depending on how they read the circumstances.

So in this tool that I mentioned before, one of the things that we've put out there, taking a page from crisis and emergency risk communication, is that it's really important for the sake of clarity to talk about what you don't know -- what you know, what you don't know, and what you're doing to find out.

And I think what you're doing to find out is a really

important thing. So if you think about, you know, an emergency response and the first person who stands up to talk about that, that's what they're doing. It's like they're saying, you know, we've had this outbreak, we've had this earthquake, we've had this flood, we've had this whatever. This is what we know about that. This is what we don't know, but this is what we are doing to find out, and we will be back in a certain amount of time.

So I think if we're talking about context, one of the pieces of context that we haven't talked about that we've kind of assumed is that both prescribers and patients even understand the research that's underlying this and why it has or hasn't happened.

So I think even backing it up a little bit more and thinking about how that framing of what the research enterprise is about, and I think we can do that in a clear and understandable way, provides some context for understanding why we don't have answers to some of these questions, why there is such a high level of uncertainty. And in that context then, what are the things that are known, what are the things that are unknown, and what are the things that we're doing to find out?

DR. BLALOCK: Dr. Cappella.

DR. CAPPELLA: So I want to agree with what was just said because I think that is -- that's right on. I think there have

been two comments that might help contextualize the information when there's maximal uncertainty to prescribers. And one set has been identified by Dr. Berube in terms of benefits first, the other by Dr. Baur associated with questions, with information about the scientific process.

But there's a third component of context that could be provided, although it may be too long to be provided, and that is that Dr. Blalock made clear that there is a baseline information -- there's a baseline level of risk to the fetus, regardless of whether there's any drugs involved at all. And that information is pretty clear. And so that information helps to establish some of the scientific basis.

The other kind of baseline information that might help contextualize what comes next might be the baseline risk to a woman who is experiencing disease or negative consequences in terms of her vulnerability and severity. And Dr. Wisner, this morning, I think made a very interesting point about her counseling sessions.

She says -- she said, if I paraphrase correctly, that she begins her counseling session by telling the woman forget about, for the moment, that you're pregnant and just consider the consequences of the disease that you have and how we could treat it if you weren't pregnant.

Again, that's clear-cut scientific information that helps establish, I think, some of the science base for what then

comes next, which is here's what we don't know, and now we can tell you about the pros and the cons of the information that is out there.

So part of what I'm searching for is a way of -- and I'm sort of pulling together some strands here. Part of what I'm searching for is a way to ameliorate, mitigate the consequences that come from maximal uncertainty with the next set of information, which is we don't know how this drug is going to affect a pregnant woman. There's pros, there's cons, there is reliable, unreliable, robust, non-robust, consistent, inconsistent information.

So I guess the big issue for me is how to mitigate, how to ameliorate what comes next in the cases of maximal uncertainty.

DR. BLALOCK: And I think I probably do need to call us for a close today. You know, I was given an option a little bit ago of whether we wanted to stop right at 5 because the cabs could have been, you know, brought at a different time, and I said no, no, no, we're going to stop at 5. So we either stop, or I'll walk back to the hotel.

(Laughter.)

DR. BLALOCK: So given that, great discussion. We'll come back to this question. We've got a list of about six people who have questions. So we'll start, you know, we'll pick up right there tomorrow.

So I want to call the Committee, the FDA and -- oh, I want

to thank everyone, you know, for their contributions today. And I call the meeting today for a close, and we pick up tomorrow at 9 a.m.

(Whereupon, at 4:57 p.m., the meeting was continued, to resume the next day, March 6, 2018, at 9:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

RISK COMMUNICATION ADVISORY COMMITTEE

March 5, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration.

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TIMOTHY J. ATKINSON, JR.

Official Reporter