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 6, 2018
9:00 a.m.

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

PANEL MEMBERS:

SUSAN J. BLALOCK, Ph.D., M.P.H.	Chair
CYNTHIA BAUR, Ph.D.	Member
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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M E E T I N G

(9:00 a.m.)

DR. BLALOCK: And so I would like to call this meeting of the Risk Communication Advisory Committee to order. If I can get everyone to have their seats.

I'm Dr. Susan Blalock, and I'm the Chair of the Committee.

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 today's meeting have received training in FDA laws and regulations.

Before we begin, I'd like to ask our distinguished Committee members and FDA staff seated at the table to very briefly introduce yourselves and state your name, area of expertise, position, and affiliation. So I started this way yesterday, so I'll start with Lee today.

DR. ZWANZIGER: Lee Zwanziger, FDA Risk Communication Staff. I'm the Designated Federal Officer of the Committee.

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

DR. PLEASANT: Do not ask me where the buzz is coming from. Andrew Pleasant, health literacy media. We work to prevent chronic disease in low-income, underserved communities.

DR. LYERLY: Anne Lyerly. I'm a Professor of Social Medicine at the University of North Carolina at Chapel Hill, Research Professor of OB/GYN, and Associate Director of the

Center for Bioethics. My research is on ethically complicated issues in reproductive medicine.

DR. SLOVIC: I'm Paul Slovic, University of Oregon and Decision Research, psychology, and I study the psychology of risk.

DR. HOWLETT: Elizabeth Howlett, Washington State University. I study judgment and decision making within the context of consumer health and welfare.

DR. CAPPELLA: Joseph Cappella, Annenberg School for Communication at the University of Pennsylvania, communication media and message effects.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant, patient representative for chronic daily migraine, arthritis, fibromyalgia, and chronic pain. I'm also a sociologist who's done work and talk in social institutions and people processing institutions.

DR. TRACY: Jim Tracy. I'm an Associate Professor of Pediatrics at the University of Nebraska. I'm also in private practice in Omaha, and I'm on the Pulmonary and Allergy Drug Advisory Committee.

MS. DUCKHORN: Jodi Duckhorn, Director of the Risk Communication Staff. Good morning.

DR. NGUYEN: Good morning. Christine Nguyen, Deputy Director for Safety with the Division of Bone, Reproductive, and Urologic Products.

DR. YAO: Good morning. Lynne Yao, Director of the Division of Pediatric and Maternal Health, CDER.

DR. RIMAL: Rajiv Rimal. I'm at George Washington University, and I study social behavior change.

DR. WOLF: Michael Wolf, Professor and Associate Division Chief, General Trauma Medicine, Northwestern University.

DR. WINTERSTEIN: Almut Winterstein. I'm Professor and Chair of Pharmaceutical Outcomes and Policy at the University of Florida, and I'm also Chair of the Drug Safety and Risk Management Advisory Committee to the FDA.

DR. SNEED: Jeannie Sneed. I'm currently a consultant, and my area of expertise is food safety.

DR. NAHUM: Good morning. Gerard Nahum. I am Vice President of Clinical Development at Bayer Pharmaceuticals. I am also a member of the Bone, Reproductive, and Urologic Products Advisory Committee, and I'm an obstetrician/gynecologist by training.

DR. KREPS: 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 in society.

DR. SPONG: Good morning. Cathy Spong. I'm the Deputy Director at Eunice Kennedy Shriver National Institute of Child Health and Human Development. I'm an obstetrician/gynecologist and maternal-fetal medicine subspecialist. I'm also the Chair

of the Task Force on Research Specific to Pregnant Women and Lactating Women, and my research interests have been both -- span from basic science and neuroprotection through clinical research in pregnancy and lactation.

DR. BERUBE: I'm David Berube. I'm a Professor of Science and Technology Communication at North Carolina State University and currently Co-Director of the Research Triangle Nanotechnology Network.

DR. BAUR: Cynthia Baur, Professor of Health Literacy and Director of the Center for Health Literacy at the School of Public Health, University of Maryland, and expertise is health literacy.

DR. DIECKMANN: 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, biostatistics.

MS. ROBOTTI: Hi, I'm Suzanne Robotti. I'm the Founder of MedShadow Foundation and the Executive Director of DES Action USA and the consumer rep on the Drug Safety and Risk Management Committee.

DR. LEE: Hi, my name is Charles Lee. I'm senior advisor on health literacy and language barriers at First Databank. My area of expertise is health information technology and communication with patients with limited English proficiency.

DR. BLALOCK: And, Dr. Goldman, could I have you introduce

yourself?

DR. GOLDMAN: I'm Dr. Myla Goldman, and I'm at the University of Virginia. I'm an Associate Professor of Neurology, and my area of care and research is in multiple sclerosis. That's it. Sorry. Thank you.

DR. BLALOCK: And Lee Zwanziger, the Designated Federal Officer for the Risk Communication Advisory Committee, will make some administrative remarks.

DR. ZWANZIGER: Good morning. I will read the FDA Conflict of Interest Disclosure Statement into the record. It's the same statement that was read yesterday; however, I will proceed with reading it into the transcript.

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 government employees 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 conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Committee who are special government 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 or, for purposes of 18 U.S.C. 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, or 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 Committees, as shown in the meeting roster. Except for the Industry Representative, as noted above, those 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 products or firms not on the agenda for which a 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 returning the meeting to Dr. Blalock, I'd like to make a few other announcements.

Handouts for this whole meeting are available at the table outside the meeting room.

The FDA press contact is Sandy Walsh. And if you would like to speak to her, let me know. Members of the press, please sign in at the sign-in sheet outside.

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

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

Thanks.

DR. BLALOCK: Thank you. We'll now proceed to the second Open Public Hearing portion of the meeting, but we don't have anyone signed up in advance. Does anyone in our audience wish to speak to the Committee at this time? If so, would they approach the podium?

(No response.)

DR. BLALOCK: Okay, barring any comments, I now pronounce the Open Public Hearing to be officially closed, and we'll not take any additional speakers for the remainder of the meeting, and we'll now proceed with today's agenda.

I wanted to start. You know, we spent a fair amount of time at the end of, you know, yesterday's meeting discussing Question 1, and I thought I put a fair amount of time, you know, thinking about the issues that we discussed yesterday and kind of summarize some of the main points in the effort of trying to move the discussion forward. I do have a list of folks who had raised their hands to have comments before we ended yesterday, and I'll go through that and give folks an opportunity to see if those, you know, comments are still relevant.

Some of the other questions that we have, you know, to address during the remainder of the meeting are pretty meaty, and so I'd like to, you know, get into them and move forward as quickly as possible but without shortchanging anyone who has

important remarks to make.

But with that as a little bit of background, I actually came up with what I thought might be three, you know, recommendations that we might want to make, you know, to the FDA just based on the discussion that we had yesterday, and the first relates to all of the uncertainty, you know, that exists in this area. And, you know, we talked yesterday to a fairly large extent about, you know, the lack of data and, you know, the uncertainty and I think the -- you know, sort of a just principle in all of this is that the more uncertainty that there is, you know, the harder the challenges for communication. And that's why it's, you know, somewhat relevant to our discussion here, which really should be focused on how we communicate the data that we have in hand.

So I think that what I heard yesterday is, you know, a lot of folks saying that we really do need more data. You know, the more uncertainty that you can address and reduce, the greater the uncertainty that you can reduce, the easier it will be to communicate the information.

And we also heard that there are about six million pregnancies in the U.S. each year. That's a lot of exposures, so there's lots of data out there. You know, we live in an information age, and it seems like there should be -- oh, one other thing, that when there's a lot of uncertainty present, and I think that Dr. Pleasant made this point, that it has the

potential to increase public cynicism, you know. Well, you know, they don't know what they're talking about; you know, they're just sending mixed messages. And so, again, just a call for more data. So I think that even though it's a little bit outside the scope of this Committee, I'm hoping that everyone would agree that, to the extent possible, that there can be initiatives that reduce the uncertainty around the medication risk as well as the medication benefits during pregnancy, that that should be a priority in this area.

So that's my little speech on that issue. Let me just ask, is there general consensus that that is true, that that is a recommendation that we would like to make, just the need for more data? Okay, I'm seeing a few head nods. And, again, I'm trying to push the conversation ahead a little bit. Let me just ask if anyone has a strong disagreement with what I just said. Okay, I see one hand.

Dr. Nahum.

DR. NAHUM: I'm sorry. Yeah, Dr. Nahum. I think you're absolutely right, there is a need for more data, but in the absence of that data, we still need to come up with a strategy, and to collect the type of data that you're alluding to is going to take some significant amount of time. And so I wonder, in the interim, if we don't have a charge to come up with something to fill that gap.

DR. BLALOCK: Absolutely. And I did not mean to convey

anything otherwise; we have to live with what we have today.

Dr. Spong.

DR. SPONG: Yeah, I think the comment that I was going to make, I don't disagree with what you're saying, but I don't know that it's really in the purview of what they're asking us today, of whether or not we need data. Everything's pretty clear; data is needed, and it is not going to be rapidly obtained despite all of our best efforts. So I think what we're trying to do is to figure out how do we communicate with the information that we have, given the requirements of the FDA.

DR. BLALOCK: Dr. Baur.

DR. BAUR: So Cynthia Baur. I would agree with that statement, and I think it's a little bit beyond what we were asked to do, but I also -- I'm not sure that I accept that uncertainty inherently makes communication more difficult and certainty makes communication easier. So that, I think, might come up, you know, earlier, and so if that's part of the preamble, I guess I would take issue with that.

DR. BLALOCK: Dr. Pleasant.

DR. PLEASANT: I have the interesting microphone today. I actually don't know that I said that, but if you wanted to interpret what I said that way, that's fine. But I think Cynthia has got a point that's worth paying attention to. What I'd like to do is actually push it a little farther, though,

because I know what we've been asked to do is one thing, but strategically labeling can create an influence upon the field to incentivize people to create that stream of data, and I don't see -- even though it is beyond the "question" we were asked, we get to say whatever we believe and why not be strategic about developing? It will take a while, but if you don't start today, then it will take a while longer.

DR. BLALOCK: Okay. And I've got -- Dr. Lyerly.

DR. LYERLY: So two --

DR. BLALOCK: And, you know, again let me stress that this really is beyond, you know, what we've been asked to do today, and to some extent, the reason I started here was to lay this to rest and move on to what we have been charged with doing.

DR. LYERLY: So just two things. One, sort of thinking about what Dr. Baur said, and it seems to me that it may be helpful, in the context of communication about the data that there is, to be explicit about the fact that more data is needed before we can be definitive about it, and if there were some standardized language the way that there is standardized language about miscarriage risk, that might be a helpful sort of caveat for people who are going to be reading the label.

The second point: And, again, I feel like this may be beyond the purview, but I was surprised to hear that there is no requirement to report and an inclination not to report inadvertent exposures in the context of trials, and while that

may be out of the edges of our purview, it does seem to be -- you know, have something to do with what the FDA can do. So I just, you know, for the record want to say that I think that that's an important space where there may be some information that could be shared and would be very, very informative to people who are making decisions.

DR. BLALOCK: And -- oh, Dr. Nguyen would like to respond to that.

DR. NGUYEN: Hi. Just to clarify, when there are inadvertent exposures in a clinical trial and the woman, say, is discontinued from the trial, usually that woman's followed up as long as possible and FDA does receive those data. I think the main thing that was brought out yesterday was those cases don't occur frequently because there is obviously contraceptive requirements and what have you in the trial. So the limited number of patients exposed to the drug and followed, you know, to the end of her pregnancy is such that it doesn't provide for robust data to go into labeling. But the outcomes of these patients are reported to us and are reviewed.

DR. BLALOCK: Dr. Howlett and then Dr. Cappella, and then I'm going to move on.

DR. HOWLETT: Elizabeth Howlett. I just wanted to go on the record as well to say I agree with what Dr. Baur has said, and we're in a situation where we have less than ideal information. However, I think the science is pretty clear, is

that there are ways to present, you know, ambiguous, difficult, uncertain information in a more clear way, and I think that's important.

DR. BLALOCK: And absolutely, one of the questions that we'll come to address that exactly.

DR. HOWLETT: Right. And my second question, though, is it seems like we're talking about what the FDA has available, and just sort of a point of clarification. Are there other systems that we could perhaps lean on in the European Union, Western Germany, England -- surely we're not reinventing the wheel here -- that we can turn to other databases that perhaps exist? So I mean that's a question I don't know.

DR. BLALOCK: And Dr. Cappella.

DR. CAPPELLA: I just want to say something about uncertainty, and that is there's always uncertainty in data that we have, but there are degrees of uncertainty, and it's -- we know a lot more about how to communicate certain kinds of uncertainty where we can say, for example, there was a probability plus or minus a certain kind of confidence interval, and we have clear notions about that.

What we're facing here, it seems to me, is a high degree of uncertainty where there is disagreement about the evidence base, there's disagreement within the evidence base, and it's there that I think we have had the least amount of attention in the research literature where the core uncertainty is an

uncertainty of disagreement, unreliability, lack of robustness, and that is a very real challenge. But I think we know how to communicate certain kinds of uncertainty, but some of the kind that we're talking about here is more difficult, and that's our challenge.

DR. BLALOCK: The second theme, I think, that I heard yesterday, you know, we talked a lot about putting the risk in context, and yeah, I think that there's also a need to, you know, understand the context in which people are using, you know, the information, and that came through in some of the presentations yesterday. And, you know, there are lots of different risks out there, and I forget exactly who made what point, so I won't name anyone, you know, by name.

You know, when -- oh, and can we show Question 1, because that actually is what I'm referring to. When we talked about the context -- and I think that, you know, part of what the FDA is doing with the new labeling is to provide more context, you know, the background risk during pregnancy, the risk of not taking medication, and I think that those are all steps in the right directions, and I will, you know, allow folks to disagree with that.

Someone mentioned, also, the need to consider economic and culture in here. So, you know, a lot of clinicians are risk averse and, you know, someone mentioned that if they prescribe a medication, then they're taking the risk, whereas if they

don't prescribe the medication, then it's the patient that has the risk of the outcomes. So one of the things -- so I guess the recommendation is that, you know, here we're focusing on -- not exclusively on the regs related to the PLLR, but it seems like the FDA can also do a lot as part of a broader initiative to help people know that that information is there, how to use the information, and a lot more in terms of how to, you know, communicate risk information.

Again, I think it's probably our focus here, I think, is on the PLLR, but I think that it makes sense to remember that that labeling is just one thing that may have minimal impact on provider decision making, which is what the question is here, you know, and that you need to think about it in terms of a broader initiative that helps people use the information and perhaps deal with those other issues that they may be grappling with when they're trying to apply the information in their practice.

So, again, I don't want to pull us into an aside, in a different direction. Is there any strong disagreement with that? And, again, I think it's a little bit beyond our purview here. Okay.

DR. BAUR: Could you just state what the recommendation is?

DR. BLALOCK: Yeah. Just that even though I think that most of our discussion going forward today will be fairly

focused on the PLLR and those regs, but there's really a need to think about that as one piece of a broader initiative that helps people use -- that helps physicians use the information, how to integrate it into patient counseling, developing patient education materials that go with the professional materials, maybe helping people understand how to interpret risk information; that's the recommendation. Is that clear? Okay.

Dr. Joniak-Grant.

DR. JONIAK-GRANT: Hi. Elizabeth Joniak-Grant.

This sort of straddles, I feel, like what you're talking about, and this discussion I kept going back and forth with, when should I bring it up, but I think this might be a good time. When we're talking about how risk perception impacts provider decision making, I think when we're talking about context, I think it's important to remember that many patients think risk in pregnancy can be mostly controlled. They might look at background risk and you hear things like, oh, well, that's by -- because they ate this or they drank this or they did that or, you know, those types of things. And then others think there's lots of risks that you just can't control. But for both groups, you see this all the time.

You can't control what drugs you take and you should. You see comments like, wow, you can't even have a cup of tea; imagine what a drug could do, especially if they're not certain about it. And I think of things that kind of make patients see

a drug as more risky, and this could maybe help with the labeling, and that's why it kind of straddles a little bit is if it's a newer drug or they think it's a newer drug, they're not familiar with how long it's been around, lack of sort of financial, physical, and psychological resources. If their child is born with a birth defect, how am I going to do this, how am I going to manage this? Having a chronic illness themselves, they know kind of like what to expect and might sort of catastrophize a little bit with that. And then, also, if the provider is flippant, yeah, that's fine; no, you shouldn't take it and, you know, doesn't want you to ask any follow-up questions, you know, that can really cause problems.

So given this, right, it's better to have -- you have to have great benefits. And then there's a few other things, I think, that will kind of go more towards the thing, so I'll leave it there. I'll leave it there for now.

DR. BLALOCK: Just again, in the interest of time, I'm going to go to the third sort of general thing, and I think that this will probably be the least controversial that, you know, we talked -- Dr. Slovic, and I'm certain I've got your name right there -- you know, mentioned the different ways that you can think about risk, just the term "risk." And so you know, clearly, language makes a different order, that you present information that makes a difference. Clearly, information needs to be clear, and I think that we will, you

know, discuss that in some of -- if folks can look at the questions that are coming up, you know, some of those address that specifically.

You know, the point that I want to make, and I think that everyone will agree with me, is that one of the things I think that really should be a priority for the FDA is requiring user testing before these communication messages are released. And I know that there are a lot of barriers to doing that, and it doesn't fit, you know, really within the current paradigm for doing things, that you run out of time, you know, at the end. But in the same way that you wouldn't release drugs without testing them, messages should not be released without testing them. And so I know that that's not going to happen today or tomorrow, but I think that it's something that really should be prioritized, and maybe we need a new paradigm.

Does anyone disagree with that at its essence?

Dr. Spong.

DR. SPONG: Thanks. I think it would be ideal to be able to test all kinds of things, and testing communication and making certain that what it gets across is what you want it to get across is ideal. That said, I don't think we can wait to test messages, and I don't think we have to -- I don't think it would be appropriate to require that they are tested before we put them out there because there's already things out there, right? The labels are already out there, people are already

using it. What we're here to do is to try to figure out how to optimize that label, and part of that testing is what we're required and are doing today and what was presented yesterday morning, where people commented and had done surveys and communications about how effective is that current label and how can it best be tweaked. I think things can always get better, and it is lovely to be able to test them and make certain that it's working, but it's only going to be useful in that group that you're testing it in. It doesn't necessarily mean it's fully applicable. So I think you could say it would be ideal to test things, but to require that at this point, I think, would really be unfortunate.

I think one of the things we've talked a lot about, uncertainty and uneasiness with the data, you have to understand, pregnancy is full of uncertainty, and we are often counseling women about things. I think a great example is Zika, right? Well, we're counseling women, and we don't have the information because the information isn't there yet. We're used to that. We need to give the FDA the best information we can on how to optimize this label, but I'm uncomfortable saying that it must be tested before it gets changed.

DR. BLALOCK: Dr. Slovic.

DR. SLOVIC: Yes. Certainly, testing takes time and effort and money, but you can do this relatively quickly, and you can do it at different levels. One, you could test the

general concept of this PLLR kind of the structure and some of the key challenges in communicating, like when you don't have human data and you're relying on animal data when there's inconsistency. There's a few basic elements here. My intuition based on other work that's been done, going back to when they first suggested that radiologists ought to be studied as to how they were diagnosing, you know, things from x-rays and they found, you know, a wide range of disagreement among radiologists looking at the same film and they found unreliability, lack of validity. My intuition is that this PLLR, as it's presently designed, is so difficult to communicate and understand that it will be very quickly seen that this is not an adequate communication device. Now, I may be wrong, but you could do that -- sure, you have to go ahead at the moment and do something, but I think a first priority that could be done relatively quickly is to just challenge the basic structure and concept of this from the standpoint of reliability and validity.

Now, validity is a question of, you know, who decides valid, but you could have a committee that could have cases where there is a general agreement as to what the right -- what the best advice would be based on this and see the extent to which it comes true with the particular design. Now, there are many different PLLRs; you'd have to select, of course, some prototypical cases, but I would put this as a very high

priority.

DR. SPONG: And if I can just comment to that. I think the FDA is required, and I'm going to ask you guys to weigh in here, I think these -- at least at the moment, they're required to have these elements. And so, sure, you can say that maybe these elements shouldn't be there, but right now they're required, if I understand correctly, and what we're asked to do here is to provide information on how do we optimize them. And I appreciate that yesterday there was information given on what worked and what didn't work, and I think what we're here to do is to try to figure out how best to advise and give some thoughts and recommendations on how to optimize it. But if the FDA could weigh in on that.

DR. BLALOCK: Okay. I was just going to say, again, I think that maybe I got us a little bit off track rather than getting us on track, so let me just kind of synthesize. And, Dr. Nahum, I've got your name from yesterday, so let me delay it for just a second and try to get us back on track again.

What I hear, I was expecting universal agreement. I definitely did not hear that, okay, so there's not universal agreement on that. There's definitely dissenting voices. Let's go back to -- those are the three points that I had to make. Let's go back to the list that I had yesterday, and we'll add everyone that we've added today and go back to the broader questions. If you do have a comment on the user

testing, you know, you can interject it there, but again, I think that that is probably not the primary focus here. And when we get to Question 2, it gets more specific about the effectiveness of the PLLRs, and we'll have lots more comments. So I've got a fairly long list. If people's comments are no longer relevant, feel free to pass because I am -- I'm anxious to get to Question 2 as quickly as we can.

So Dr. Nahum.

DR. NAHUM: Thank you. Dr. Nahum.

So I'm going to go through these in order for Question 1, because I have some notes about this, and first with regard to risk perception. There was a discussion yesterday that I thought was very interesting and robust, but I'd like to make some specific suggestions about this, and there are two concepts here that I haven't heard brought up yet.

In terms of risk, I think the points that were made by Dr. Slovic yesterday are very well taken, but there are two ideas that have been used in the past. One is number needed to treat to get an effect that is desired, and the second is the number needed to harm, in other words, how many people will be exposed to a particular drug with a particular underlying condition to result in some condition of harm, and both the effectiveness metric and the harm metric need, of course, to be defined in order to come up with those numbers. But they are both condition specific, and I would like to suggest that we at

least think about whether or not those two elements should not be included routinely in risk perception sort of labeling.

With regard to the second question, Subpart B, this is about interpretation of uncertainties of available data, and we've talked a lot about this. But the one thing I haven't really heard a lot about is the idea of individual risk tolerance, and this is something that, you know, is embedded in everybody's decision-making process, how much risk they are willing to accept. And, of course, there are different, you know, sorts of compendiums of data about this, but I think we need to bring this up as a concept, at least, in labeling.

I don't have anything else to say about Subpart C, but I do about Subpart D, and this is about benefit-risk considerations. And we talked a lot about risk of teratogenicity, and I think that's all very well and good and certainly very valid and one of the reasons we're here.

But the thing that we haven't talked about is that many medicines have more than one indication, and unfortunately, those indications are not necessarily for commensurate types of underlying diseases. I can, off the top of my head, think about an antibiotic or two antibiotics that had six different indications in their label, and I would tell you that the severity of the different conditions for which they were approved to treat is vastly different. Now, the risk profile for the treatment by the antibiotic may not be terribly

different, but this enters into the benefit-risk calculus, and each of those are really condition specific. So that's something that I think the FDA needs to take into consideration when coming to recommendations or assessments with regard to benefit-risk. They are not necessarily uniform for particular products across all indications.

And then, lastly, I just want to echo what people have said about Subpart E. I practiced for quite a while, and I would say that I think that the general perception of practitioners is that the risk of omission in terms of medicolegal liability is relatively low as compared with the risk of commission. In other words, if you prescribe something and there is an adverse outcome and it is a known risk of that particular product, that will almost certainly come back to, you know, require some degree of explanation on your part, whereas if you omit some kind of treatment and say that you did not believe in your benefit-risk calculus that it was indicated for a particular patient, then typically the medicolegal risk is considerably lower. And I think other people have said that, but I'm not sure they put it in the framework of omission and commission, so I thought I'd say that. Thank you.

DR. BLALOCK: Dr. Winterstein.

DR. WINTERSTEIN: Yeah, I would like to elaborate a little bit on the whole contextualization discussion, and that fits very well in what Dr. Nahum just talked about. The idea to

contextualize risk for patients is a very important one, and it's clear that physicians or any healthcare providers are in a good position to do that. I'm not sure the FDA is, and for similar reasons that were just touched on, and that is that that benefit is very variable. And I would like to share an example.

So imagine an antibiotic that is used either to treat a urinary tract infection or an endocarditis in a pregnant woman. The decision is very different, and the benefit is very different, and the FDA would have no means of providing the variety of different scenarios that would need to be considered in order to make a risk-benefit decision. For that particular patient, the antibiotic is the same.

The other example that I have is an approval decision or a discussion that we had surrounding topiramate for the treatment of obesity. Topiramate was approved as an anti-seizure medication many years ago, with no REMS, no medication guide, even though it causes cleft palate. The idea here was that these are patients who are treated by neurologists, the underlying disease is difficult enough, risk-benefit decisions are clear, therefore, there is no additional risk communication needed other than what is in the label. Topiramate is being used off label for everything under the sun from -- well, we all know it. So the communication related to the context of treating seizures is completely irrelevant considering that the

drug is used, in its majority, not for the treatment -- not for the indication that it was originally approved for, and now we have an approval decision for the use of the same drug in combination with phentermine to treat obesity in young women. So that particular approval decision actually ended up including a REMS where patients do need to be informed, and so there we have a medication guide for the same drug for two different indications.

So, you know, considering an example like that, I think thinking about how to contextualize in the label is almost impossible and impractical and will very quickly be very outdated.

DR. BLALOCK: Dr. Lee.

DR. LEE: So when this slide says decision making by the healthcare provider, I see the workflow in terms of two broad categories. The first is pruning the list of therapeutic options. And I think this goes back to the survey result that Dr. Namazy presented, where 62% said it was not helpful in the new labeling form because this -- although this new narrative format makes it easier or more inclusive to have that discussion about whether to take the drug or not take the drug and the risks associated with it, I don't think it's as helpful in terms of pruning down the list of therapeutic options down to the safest ones, although that might be an area for discussion.

So the other thing that was presented was, I guess, the Quick Take option where you get a summary of very -- a one-sentence summary of what the study results implied and then having that at the beginning of the narrative so that if a physician wanted to kind of glance across the list of therapeutic options to make a decision choice and narrow it down to two or three, I think, would be helpful. But I think having or requiring the physician to look at and read everything for 20 different drugs, I think it's going a little bit too far and making it more difficult than being helpful.

DR. BLALOCK: Dr. Spong.

(Off microphone response.)

DR. BLALOCK: Dr. Slovic.

DR. SLOVIC: Yes. With regard to the benefit-risk tradeoff, I was just thinking that along with the challenge of uncertainty, that when there are, say, two drugs that would treat a certain condition like seizures, epileptic seizures, and one is an old drug that's been around a long time, presumably then you have the benefit of the experiential knowledge of use of that drug. One's a newer drug that I wonder if anything can be said about the -- you know, go first with the older drug and see if it works before the new drug, in the face of uncertainty.

DR. BLALOCK: That's a very good point, and I thought about that as well, sort of something that would indicate the

track record and the number of exposures.

Dr. Kreps.

DR. KREPS: Thank you. I'm so glad you came to me because I was -- I had something that kind of hit my brain the other day, at the end of the day, and I thought it was really good, and I was really frustrated that I didn't get a chance to kind of lay it out. So my frustration actually works well because I've been germinating about it and thinking about it, and I think I've got an even better focus now. Hopefully, this sounds as good to you as it did in my head, so I'm looking for some kind of intersubjective test on this.

I was thinking about this from the sense of sense making and information processing, and there's a model that I use a lot that really makes a lot of sense to me; it's a model that came out of psychology by Karl Weick, and it's called Weick's Model of Organizing, and he basically uses a principle of information processing to guide the use model, and it's called requisite variety, and requisite variety says that you can respond to the same issue the same way. It doesn't work when you have relatively simple, unequivocal issues. You can apply rules, and they work very well. And it appears to me that the FDA wants us to help them develop good rules for, you know, providing labels, and I think that will work well for the drug information that's not equivocal, that it's pretty clear that there's good evidence and you can apply those rules. However,

when you try to apply these same rules to more equivocal uncertain information, it falls apart, and you end up making a lot of mistakes, and it's very frustrating, and it doesn't serve things well, and it actually causes more problems.

So Weick suggests that instead of applying the rules, he basically says when you're doing that, you're violating requisite -- the principle of requisite variety. You're trying to do things that don't really make sense. And so what he says is that you need to kind of find ways of processing the equivocal information, the drugs that you don't have good information about, so that you can eventually refine it so that it's clear enough that you can apply those rules.

The good news is that you don't have to always do this, that it's a process where you learn things in the processing of the equivocal information. That becomes what he calls organizational intelligence that guides you in the future, and so then you can apply rules more freely in the future and you have precedent for how to do things.

So what I'm suggesting, the sort of nice thing about this is, in my head, is that it has some pretty clear policy and practice implications, is that you identify right away the drugs that have the clearest, you know, evidence and apply those rules and do that and then take a closer look at the other ones that are more equivocal and then develop some systems for trying to make them less equivocal, make them more

certain, make them more clear, either -- gathering more data.

What I suggest that we do is that we interact and we discuss these with knowledgeable others or with reference sources, so the idea that Beth came up about are there other, you know, systems out there in Europe or other countries that you could consult to try and provide other sources of information is a great way of resolving and processing equivocality. Another way would be to enlist experts, pharmacological experts or practitioner experts, consumer experts who would provide you with feedback about what they know about those drugs that are not really clear to help you make sense of them. And maybe even have a standing board where you would use them on an ongoing basis to make your life easier, so that you can apply the rules clearly and do that. And you can try and identify, either yourself or with others, but I suspect you can probably do it yourself because I know, I can feel your pain that there are drugs out there that are driving you crazy that just don't -- are not easily classified, and you know which ones they are. You can kind of hold those and then subject them to a process. It doesn't mean you have to kind of take them off the listing right now, but you can refine them and improve them until you feel more comfortable and in the meantime develop better systems and regulations and rules. And maybe we'll come up with some really good strategies for terminology to help you with that here, but you

can use that in the process to try to make this easier.

But what I'm really worried about is the -- you know, the force, because there's the demand to get this done. And this happens all the time in organization. We have the demand to get it done, get the product, run the campaign, you know, sell the product, get the list of drugs that we end up -- even though it doesn't fit and the process doesn't work, we do it anyhow, and it's very uncomfortable, it doesn't feel right to you, and it also doesn't work very well, and it may end up complicating the prescribers' jobs in terms of what to do.

So what I recommend is that you try to, you know, resist that violation of requisite variety by coming up with some systems to triage and segment the different drugs into categories, easily communicated/not easily communicated, and then figure out ways of trying to transform those not easily communicated drugs into a state where they are more easily. Some of that can happen quickly, and some of it may take a lot of time, but in the meantime you're going to do a better job; you'll have better communication, and it will be utilized more effectively.

DR. BLALOCK: Thank you.

Let's see, Dr. Robotti.

DR. KREPS: You're not going to let me get feedback on that?

DR. BLALOCK: I'm worried about time.

DR. KREPS: Okay, all right.

DR. BLALOCK: I'm really worried about time.

Dr. Robotti.

MS. ROBOTTI: Hi, this is Suzanne Robotti.

I'm not really happy about the phrasing in the question, "the healthcare provider decision making and patient counseling." It doesn't seem to really be emphasizing the shared decision-making process.

I do believe that there's data out there that we're not using. And forgive me, I am not an expert, but I do know that there are drug pregnancy registries that have been out there for years, and I wonder if maybe that information shouldn't be listed, what information we do have shouldn't be listed right on the PI. A patient hearing that 5,000 women have gotten this drug over the past 8 years that it's been on this registry, or 5,000 women have registered on this registry over 5 -- over however many years, and there have been, you know, a baseline equivalent of the background, you know, congenital anomalies. I hope that was in English; I hope I said that right. But, basically, it would help that patient to know that, you know, X amount of other women have taken this drug and, you know, there were zero two-headed babies born and, you know, the number of defects were either in line or not in line. Even though you may need 20,000 people to study to find those defects, it would still give some level of context, I believe.

Pre- and post-data testing or pre- and post-testing of these messages, we've already got a study that says it's not working, it is difficult, the doctors don't like it, it's not doing its job. What more do you need? Honest to God. The compromises I am seeing on this Committee offend me. We don't have data. Women have been getting these drugs for decades. We've got pregnancy registries, we've got people already taking the drugs; study the people who volunteered to take the drugs, get the information. We have studies that are not reproducible, yet we accept the data -- or haven't been reproduced, we accept the data, and now we don't want to test the message. The compromises here are too many. People get harmed. People don't get the care they need; people get too much care.

Forgive me for being highly sensitive to this. As a DES daughter, I know what happens when people are given a drug that wasn't correctly tested, that wasn't correctly communicated, and can cause generational issues. I don't want that to happen again, nobody wants that to happen again, but we're treating these people in the dark, and that's not fair and they don't know it. These patients need to know that you guys are just guessing.

DR. BLALOCK: Thank you.

Dr. Rimal.

DR. RIMAL: I want to come at it from a slightly different

perspective. I feel, you know, going back to our charge and the PLLR --

DR. BLALOCK: Dr. Rimal, if you have something to respond to this question in front of us, that's great. But I'm really trying to move us on to the next question, which is, you know, really relevant to the charge. So if you can really -- do you have something to respond to these questions?

DR. RIMAL: I don't think I would be speaking if I do not think I did.

DR. BLALOCK: Okay.

DR. RIMAL: So the PLLR asks us, for the charge of the Committee, to think of the prescribing person, the provider, as the target audience. And that, I think, is a manifest target audience, whereas the true target audience, the people we really care about, of course, are the pregnant and lactating women. In the context of what we're talking about, I see two target audiences. One is how does the FDA communicate with the providers? And the second is how do the providers communicate with their pregnant and lactating women? And related to that, and I believe where the focus of our discussion should be, is how do we empower the FDA to empower the providers to be effective communicators? Yes, they're dealing with uncertainty, they're dealing with a lot of unknowns, etc., etc., but we haven't really focused on how do we empower the physicians to be effective communicators.

And I think Dr. -- I'm sorry -- Robotti just talked about shared decision making, and that is a wonderful scheme that we can use to promote that, to empower the physicians to be effective communicators and to help them in that process so that women, at the end of the day, are making the decisions themselves, but they're being empowered by having been provided effective communication.

DR. BLALOCK: Thank you.

Dr. Baur.

DR. BAUR: I'm waiting for Question 2.

DR. BLALOCK: Okay. Dr. Goldman.

DR. GOLDMAN: Okay. Oh my. So a couple of things, I guess. One is I thought that we were the user testing, like I thought that was sort of the point of the panel was they've been doing it, there's 500 labels done, and we are the focus group, we're here as communication experts, prescribing physicians, so that's kind of our job here, was my interpretation. I don't know that we need more than that.

I wanted to just offer, and I made some offhanded comments and was told sort of the importance of sharing this, but I think that we are operating in the dark, and we know that we're operating in the dark, and as such, we are making choices of omission. And I just want to share with you, I think, to bring this back to kind of why we're here, what is actually happening.

So the disease that I care for is multiple sclerosis, and these women present between the ages of 20 and 40. Often they present immediately postpartum, and then they go on drugs that are all biologics and without any clear data regarding pregnancy. And, predominantly, the field that I practice in is men. And so these women make two critical choices in their life. Their first is whether or not to have a child, and then the second is whether or not to breastfeed that child, and in both of those decisions, they are forced between choosing to go back on a drug that keeps them walking, talking, and caring for the life that they just created, or not going back on that drug and risking the ability to be a mother, right? So these are forced choices, and this is what's happening every day.

In another context, and in conversations that I had with other advocates, some of these women are not making the choice that I deal with, which is the ability to walk versus, you know, having a second child, but potentially they're killing themselves because they don't have their drug because the label says we don't know if it's safe and the doctors are not giving those drugs. So we are already operating, these women are all living in the dark, and our job here is to, through whatever it is, a little crack in the baseboard or opening of the shade, right, for every therapeutic room we're going to have a different amount of light to bring in. But what we want to do is bring in whatever amount of light we have so that we can

guide these people, and for each one it's going to be different, but that is our task here.

So I just wanted to share with you, I think, the other side of this. I have seen women who were told they had to stop their MS therapy 3 months before they tried to start getting pregnant, which meant that they were off drug for 9 to 12 months total, who had a catastrophic event, ended up in a wheelchair and not pregnant and unable to care for their first child. This is the reality of what's happening. These are 30-year-old women, 40-year-old women, who are no longer able to work, who require full-time care, who then have their children who require full-time care. I mean, just to bring the scope of this out.

And the last story that I'll share is I was at a national meeting where three thought leaders in my field were speaking to a room of physicians about caring for patients with MS, and they said to their colleagues, with all of the cognitive authority that we bestowed by putting these men on the stage, that all they needed to tell their patients to do was to nurse for 3 days because the colostrum was all that mattered and then immediately put them back on their drug and don't let them breastfeed.

So this is the kind of thing that's happening every day out there because every label for every drug I prescribe says nothing is known about lactation. And I have some comments

about that in Section 2. But I felt compelled to share, kind of, the real world.

And then the last thing I wanted to comment on is that I agree that there is a lot of information, potentially, regarding pregnancy, and I spoke about this with Dr. Yao, and I wanted to just put it on the record that I think there is an opportunity for the FDA to sort of codify how that information is given from pharmaceutical companies and to look at sort of class effect; so you may have five people on one drug, five people on another drug, but they're all triptans or something where we can start to pool these together.

But the problem that we need to recognize is that that requires time and money, and right now, the structure that we have in place depends on nonprofit and NIH funding to collect this data. We do not have a system in place for our government to collect data on these women, and so that requires more than is what is in the scope of this. Our entire system is not designed to capture and collect these women, and to say that we should or that it's important is not going to get us there. We'd have to completely make efforts to restructure how we do clinical research related to these issues.

DR. BLALOCK: Okay. I've got four more comments here, and then we really need to close the discussion. And, again, if we can kind of focus on, you know, this question. The names that I have are Dr. Lyerly, Joniak-Grant, Tracy, and Dieckmann, so

I'll start with Dr. Lyerly.

DR. LYERLY: Thanks. I'll try to be brief. So three quick points: The first has to do with this question about testing, and I agree that there is some evidence, some good evidence to show that it is not working. But I think one of the problems going forward -- I like evidence. I think one of the problems going forward testing the approach any more is that there seems to be a lack of uniformity of language used in the labels that we've seen so far, and I totally understand the move to try -- the efforts to try to move away from a sort of major interpretation of what is said, but -- and I think maybe this comment can be brought later, but I think testing may have a role if we get to a point when we have more uniformity of language, if that becomes something that the Committee decides is an important thing to do.

The second is -- has to do with two points that were on the list here. One has to do with this question of omission and commission, and I think there is clearly a view out there that there is a higher risk of being sued or having liability -- and Dr. Spector-Bagdady could speak to this, I imagine -- by giving a drug but then by not giving a drug. But you can imagine that somebody who is debilitated by a physician's refusal to prescribe a drug in which there is no data could also result in a lawsuit, and if you look at the delivery context, the reverse is true. So the decision to do a

C-section, people feel like it's less risky for them, as physicians, than the decision not to do a C-section. So it flips. So I guess there's a real question about whether this is a risk distortion on the part of physicians or if it's really true that these legal liabilities differ depending on whether or not you prescribe or don't, and that might be relevant to the ways that we think about the label.

The third point is that, again, I really appreciate this emphasis on shared decision making and, really, that it's healthcare provider and patient decision making, and I think there needs to be a role for emphasizing patient values here, and where risk assessments for an individual patient in her life context might be different depending on what the risks are and what -- how she thinks about them. And, again, sort of, you know, recommendations that say this drug isn't recommended for XYZ, it may put women in a place of not having access to a drug that they would actually value, that would be consistent with their own risk-benefit calculus. So maybe there is a role for emphasizing that this is a decision between the patient and the provider, and patients' values need to be considered in the risk-benefit calculus as well as these issues of background risk.

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: I'll be brief. I think looking at the benefit-risk, one thing we have to remember is that sort of

many women and sort of larger society -- and providers don't consider minimizing pain or discomfort or emotional stress as a benefit, and if they do, it's often underemphasized. Discussions center more on long-term, can't-be-undone impacts, which are obviously important, but one's comfort is often not seen as important as a neonate's health, sort of I can suffer even in the extreme for the short term to ensure the long-term health of my baby. So I think if we're talking -- as we talk more about the label, we need to be mindful of sort of suffering and how that fits in with the benefits of alleviating suffering.

And I think one thing that's important about to recognize the importance of suffering, when I look at someone like the fibromyalgia groups or people with neuralgias, there are plenty of people that say I can't, I can't manage without these drugs, I'll suffer too much, but we don't know how risky they are, therefore, I'm just not having kids. And I see that over and over and over again. Or more kids.

And then just in reference to -- with the uncertainties, I think we want to be mindful that there's sort of an assumption here that the prescriber knows all about the diagnosis, the medication they take, the benefits of said medication, how that works with other medications they're taking, and the impact this will have on pregnancy and the fetus. And this can be the case, but often it's not. Often you have a group of

specialists, your primary care provider, an OB/GYN, and you're sort of trying to move between all of them, who often don't speak to each other, and kind of carrying information back and forth to sort of figure out what you need to do while you're on a time clock and you think, gosh, could I be damaging this fetus right now or this embryo, and I don't have time to, sort of, sort this all out.

And so I think one thing that we would be mindful of when writing the label is sort be mindful that the doctor might have limited knowledge about the medication or what it treats or about pregnancy. And this is where Dr. Lee said where the Quick Take option could be really useful, especially if it's tied into what -- how you would use it given a certain indication. You know, not as strong language, but we recommend this in light -- if you're taking it for this indication. The evidence, you know, isn't maybe very strong if you're taking it for that indication. So that could be something that could kind of help bridge the gaps.

DR. BLALOCK: Thank you.

Dr. Tracy.

DR. TRACY: Yeah, I promise to be brief also. I think going back to the shared decision making, the question really is about healthcare providers. For me, the concept or the idea of a shared decision is really an ethical point, and to me, it's almost a prerequisite to the whole process. Maybe it

isn't for some, but it certainly is for me. So, really, a lot of what we're talking about is how do I, as a provider, participate in that discussion? And I kind of struggled with sort of the way we -- or the mechanism that we have to kind of convey that data, and I think that's a big piece and really, mostly we'll cover that in Question 2, which is why I'm going to stop it.

I do have one clarifying question, and it's really pretty easy. We talk about this data, this data, this big data. Where does this data come from? I mean, is it a shared opportunity between various agencies? But we talk about the data, and I know we have the registries and such, and I know we have VAERS and things like that, but which data are we talking about? And is that data shared between agencies?

DR. BLALOCK: Is that a question that you did want a response to?

DR. TRACY: I'd like the FDA to just help me out.

DR. BLALOCK: Okay, a brief response.

DR. YAO: It is shared, and we have a group that's tasked by HHS through the legislation, 21st Century Cures, that Dr. Spong actually is heading, that is tasked to look at the federal sources, bring all the stakeholders together, and figure out the best way to improve the quantity and quality of information in pregnancy and lactation.

DR. BLALOCK: And Dr. Dieckmann, and then I'm going to

call Question 1 to an end.

DR. DIECKMANN: I'm just getting in line for Question 2.

DR. BLALOCK: Oh, good. Cool. Okay, let me call Question 1 to an end because we are probably about 30 minutes behind schedule already, and I know that folks want to get -- the FDA wants to get to the other questions. So, you know, if I am abrupt with folks, you know, I hope that no one will be offended. I definitely appreciate all of your feedback. I'm just trying my best, you know, to keep it on time, keep us on the regular schedule.

So can we put Question 2 up there? And I don't think I'm going to try to summarize what we've -- I think the speakers have been -- the members of the Committee have been pretty clear in their comments. Do you feel like you've gotten what you need on Question 1?

DR. YAO: Yes.

DR. BLALOCK: Okay, great.

(Laughter.)

DR. BLALOCK: Okay. And here's Question 2, and I'll read just the beginning of this. So discuss how effective PLLR has been in conveying safety evidence in pregnancy that's useful to benefit-risk decision making. Include in your discussion the following. And you all have this in your packets as well.

We're going to try to cover 2A and 2B at the same time. So 2B is consider the following situations and discuss best

practices to communicate the following in drug labeling, if appropriate. And these four different situations -- and we're going to have to toggle back and forth between these two slides, so it's probably best if you can get the hard copy in front of you as well, and these four situations are basically based on the amount of evidence and the amount of uncertainty that's available; at least, that was my read.

So let's go back to 2A and I'm going to be very, very brief here, but just say that I've already heard -- and I really appreciate, you know, the comments from Dr. Robotti -- that there's already evidence that clinicians are having problems with these, so that's noted for the record. And I think that's all I'll say, and I'm going to leave it to you all to discuss further, and the first person that I have on the list is Dr. Baur, who waived her turn a few minutes ago.

DR. BAUR: So Cynthia Baur.

So like Dr. Kreps, I was doing some ruminating, and it seemed to me that the -- we actually have two information problems that got a little conflated yesterday, and so there's the information problem about "how," right? So that is our very specific charge and I would argue that there's plenty of people in this room and in the literature that can give you "how." We all have our own tools and techniques for "how," and you might even run a little friendly competition among us to have us give you different options about "how." But I think

this Question Number 2 sort of leads to your second informational issue, which was addressed by some of the presenters yesterday but is not explicit in the way you frame the question, and that's that you have what has been a very effective heuristic that you are trying to replace, and that heuristic is your A, B, C, D, X system.

And there's plenty of decision scientists around the table who know a lot more about heuristics than I do. But the issue is, is that your new format is not really functioning well as a new heuristic. And so you've got this heuristic that people are very attached to and that, I would argue, embodies the essence of a memorable system because it's based on the alphabet, and what's more memorable than the alphabet, other than our numbering system? So this framework that you've got, I think you've already answered your own question by saying that it can't be as effective in its current format because it's just not memorable for people, and you're trying to displace something that people are extremely attached and comfortable with.

So I think if we go back to -- and I think the other thing that got conflated yesterday is our discussion around uncertainty, because I think Question 2 then really brings us back to what you're asking us is conveying safety evidence, and that's different than uncertainty because, as everyone's addressed, there's a lot of inherent uncertainty.

So I think what my recommendation to you then is, is that addressing (i) through (iv) here really becomes a challenge in figuring out what is that new memorable heuristic that you are then going to have to create a campaign around itself to replace that A, B, C, D, X system, and that all of these things, then, are going to be in that context of what's going to make that information much more memorable, because I think you heard yesterday, and you've heard from the Committee already, that the text-based system is inherently going to be much more difficult than this alphabet-based system that people found very easy to interpret. So that, to me, I think -- you know, there were these sort of two different types of informational problems that got a little confused yesterday, and I think that Question 2, when I looked at it again today, I thought, aha, this kind of really does separate them and says that it's -- I think it's really moving to this text-based system that's creating a lot of your inherent problems here. And so I think it's asking us for recommendations about symbols or visuals or other things that are going to reduce the cognitive load of your new heuristic.

DR. BLALOCK: Thank you. Well, I'll just say -- because I was going to underscore that. You know, I definitely appreciate that there were problems with the old system, but I do wonder a little bit if you've thrown the baby out with the bathwater because maybe, you know, the gist was people thought

they understood the letters. They didn't understand in the way that you wanted them to, but I worry that something was lost in getting rid of them.

Dr. Yao.

DR. YAO: Thank you. So, Dr. Baur, thank you for your comments. I think you are very close to the conundrum that we face, but before I -- I just want to clarify that the old system was horrible, okay? Number one, all the things that Dr. Goldman talked about, patients who decided to terminate pregnancies or patients who didn't get access to drugs that would help them was exactly the problem with the old system. So it was incorrect, it was inaccurate, and people misunderstood the system and used it incorrectly. So I don't think there's any way -- and that was 20 years in the making of this final rule that said it's wrong, let's change it. What we have now is a system that's -- based, largely a framework of a narrative which Dr. Baur has described as not necessarily a great way to convey information in the context that we learned about yesterday, which is we got to make these decisions, we got to help these patients. So what I'm asking the Committee to do, thank you for sort of honing it in, is that we're not going back to the old system because the old system is bad. Let's make no -- let's not try to call it anything that it wasn't. It was a bad system, it was wrong, and we had many Advisory Committees and many task forces that told us that.

But what can we do in the current framework of the rule, which is promulgated by FDA, and they say -- and it says that sponsors must follow this. In that framework, how can we improve it such that we get to communicate these kinds of information appropriately? Tell us. We'd love to hear how we can do that better.

DR. BAUR: And just for the record -- this is Cynthia Baur. Just for the record, I'm not endorsing the old system. I'm just commenting on its utility for your end users because they thought they understood it and it was based in something that was highly memorable for them. I mean, it did lead to all the problems you identified. But I think that there is the principle, the technique of layering of information that has not come up here, and I think if that were taken to be a core principle of your approach, you could deal with a lot of the issues in the way that you -- the examples that you showed us yesterday. So I'll stop there because I know other people have things to say.

DR. BLALOCK: And I also want to clarify my comment as well. I was not suggesting going back to the old system, but before you throw something away, you know, it's useful to think were there good things about it? And, clearly, there must have been good things about it because people were using it. They just weren't misusing it. That deserves some consideration, is what have we lost with the letters that people liked, and how

can we incorporate it into this new framework?

So Dr. Dieckmann.

DR. DIECKMANN: Thank you very much. Nathan Dieckmann.

I'm going to kind of take off on a lot of comments that we've made throughout the last couple days -- Dr. Baur, Dr. Cappella, Dr. Lyerly, Dr. Lee, we've all made comments along these same lines, and the first thing is about the general uncertainty issue here, that I think all agree that it's probably not going to be really helpful for you to be -- us telling you how to present confidence intervals around odds ratios that are taken from large clinical trials or something. The main issue seems to be more about the strength of the evidence or the quality of the evidence that's actually being brought to bear on any of these issues.

And just reading over the risk summaries that you have here, you do address it in a certain way, but I can see how you're somewhat leaving it up to the prescriber to actually pull information as to the quality of the evidence by just reading the narrative summary. And it seems like there would be a relatively straightforward way -- Dr. Riley talked about some possible ways, not in the specifics, but in general, of just coming up with verbal labels of the quality of the evidence or the strength of the evidence for any individual hazard claim in here. It seems like it would be a lot easier for every hazard claim made if quickly, right next to it, there

was some kind of labeling system. And I'm not saying we're going back to the other labeling system, which seemed to kind of conflate risks; it kind of conflated the probability of a hazard with the strength of the evidence at the same time, so I can see why it's confusing. What I'm suggesting here, though, is more about a labeling system specifically for the strength of the evidence, so very quickly, at point of care, someone could look at this, look at each hazard claim, and very quickly assess the strength of the evidence that's available for that. Even if most of the drugs that you have now, it's basically going be a zero, let's say, on this scale. At least you would have a framework that could be updated, and that framework, of which everyone's familiar with, could be updated as the strength of the evidence improves.

I also wanted to go off Dr. Lee's comment here that, as I talked about it yesterday, there was kind of different audiences that are happening here. There's the point of care when someone needs to quickly look at this and make a decision about a patient that's sitting in front of them. For them, having this information about any particular hazard claim, as well as the strength of the evidence bolded at the beginning of this risk summary, would make the most sense. This document, as a document that provides more information for potentially other consumers to take and make their own summaries, makes complete sense to me that you would have this additional

information about the individual studies that were involved and so on.

So my comments have to do with the uncertainties that we're actually focusing on here, which seems to be the strength of the evidence, most of, not stochastic uncertainty around an odds ratio or something like that, as well as just simple kind of organization of the risk summary just to make it easier to parse.

DR. BLALOCK: Those are good suggestions. Thank you.

Dr. Goldman.

DR. GOLDMAN: Okay, so that was -- my last comments were emotional, and now I'm doing my practical, so good news. Okay, so I have four different recommendations. One of them is sort of an amalgam of what came out yesterday, thinking about the strength of the evidence or sort of what we think about as Level I evidence, Level II evidence, in looking at research. But I think that what we want, and we talked about this a little bit, is some sort of table where you could have a star system, like the stars of certainty or the stars of strength.

But for human data, maybe you have no stars. For animal data, maybe you have three stars. You know, for years on market versus number of case reports you get a number of stars. So something that's been on the market for 40 years and there's one case report, that's a four-star drug. So some sort of table where we're integrating and iteratively demonstrating

this, that is a point-of-care sort of flashpoint. And then potentially, electronically, you're in the online system, having a way to put those boxes next to each other for different drugs. So, you know, if I'm seeing an MS patient, I can crosstalk those boxes for the drugs that I'm considering and at least know what is the level of evidence, stars of certainty.

The second thing that I think would be helpful, from reading all of the examples, is some sort of table that cross-talks animal to human gestation. I was very confused about, you know, if it was given to the rat this many days, like is that the first trimester or the second, you know? So I think, for people who -- like a neurologist, poor, sad neurologists -- like reading that, like I didn't know what that meant or how to, you know, weigh that in.

The third point -- and I only have four again, so you're not getting nervous -- is the consistency language, so your boilerplate text has to be the same in every package. So, for example, your background rate, sometimes it says 3.6 and 7.4, respectively. Sometimes it says miscarriage -- whatever -- 3.4, defect 7.2. So it should be the exact same so that I can read that once, know it and know to skip it, if that makes sense. Not different from label to label.

And then the last thing that I feel really passionately about that we haven't talked that much about is lactation, and

every drug that I use says no data for lactation. And I'm wondering if that's a place where we could potentially put some sort of language that either talks about the half-life of a drug, so we know or anticipate that the drug would be cleared, you know, 8 hours from dosing, especially for some of the biologics, where they're getting an infusion once a month, for example. I think that would be very helpful because you could, you know, pump and dump for this many hours and then breastfeed for that many days.

But the second missed opportunity, I think, is related to molecules of similar size. So we know something, I don't personally, but people know something about what types of molecules go from the bloodstream into the milk. And so based on the pharmacokinetics of these drugs, I think there could be an opportunity to just say we don't know about this drug specifically, but molecules of this size typically do transfer into milk, or something like that. So those were all my practical comments.

Thank you.

DR. BLALOCK: Thank you.

Dr. Pleasant.

DR. PLEASANT: Thank you. It works. Thank you, technical folks. Yay.

Okay, so just quickly. I'm going to just say your goals are actually feasible and possible, even though we might be

sounding like it's not. So smile and pat yourself on the back for taking this effort on. I know, from practical experience, how difficult it is. We launched an effort called Clearly Communicating Clinical Trials. I can promise you that you can develop a protocol that will address the issues and the language that you're struggling with. Pay attention to the principles of plain language and health literacy.

I'm sure you've already looked at this, but just to put it on the record, also look at the guidelines that the European Union put out for the clinical trial summaries, both the lay summary and the technical summary. There's a lot of work already been done there from a regulatory body. So why reinvent the wheel when they've already created a lot of those guidelines for you?

Interpretability, a word I can never say and don't like because there's a lot easier ways to say that. There's also a lot of easier ways to say things about uncertainty, like we don't know enough, period. Right? We don't know enough. And so it goes to the point about the acceptability of risk. When I hear studies and people say that they disagree with us on the risk, whether it's the outcome, the severity, the likelihood, they might be trying their best to tell us that we have a different definition of what level of risk is acceptable, but nobody asked them that. They asked them to tell us do you agree with our interpretation of the risk, so they might be

trying very hard to say 0.01 isn't good enough for me, but they don't know how to say that and nobody asked. So be careful in judging. An appropriate outcome is not the target of this, and informed decision is the sole target. And if people make an informed decision that you disagree with, that's because values are involved and values are always going to be involved. The FDA's role is to provide the best evidence possible and stay out of the value argument. When that evidence isn't sufficient, the values are going to play a stronger role, right? You just are going to have to accept that in the notion of your job.

I would also suggest, in terms of helping people interpret, link to the clinical trial data source whenever you can, right? Those summaries are supposed to be online, so go ahead and provide the link. You know where they're at already. Let people look further into that information when it's available. Those just aren't there.

For the record, also, I do not miss that letter system. Do not repeat that mistake. One of the challenges here is people want to oversimplify it, and the job is not to simplify; the job is to explain complexity in a clear and usable fashion, and that means you have to embrace the complexity and not be afraid of it.

And then just to close, a very small point, but it goes to part of the problem, calling these narratives is just

technically incorrect. It's not a narrative, you're right, and the narrative, by definition, would have to have a conclusion, an ending to the story, and you can't provide that in here. You can't make that recommendation, which would actually make it a narrative. These are more of a vignette. So what you might want to think about also doing is adding a little bit of metadata up front about the limitations to what you can say, right? Help people understand that you can't -- there are things that the FDA simply can't communicate, you're not allowed to, or that the data don't exist, right? And that can be uniform across all of these, right? Here's the challenges with this document, and here are the limits, so that you help people with what you interpret later just by telling them what you can and can't do. That's all.

DR. BLALOCK: Thank you.

Dr. Nahum.

DR. NAHUM: Thank you. Dr. Nahum.

I'm going to address these points pretty much directly, but I have some other comments. I want to just say one thing about what Dr. Goldman said. She made an appeal, I think in principle, to the idea of class effects being incorporated into labeling, and I think that we have had experience that really goes both ways with this.

I will say that there was a class effect with regard to tetracyclines that was incorporated into labels of all

tetracyclines, including doxycycline, with regard to bone discoloration that simply took 30-plus years to get out the word that that was not a risk. And, you know, they're both tetracyclines; they both fall into the same class. It was giant risk for the original tetracycline; it was not at all a risk for doxycycline. And doxycycline is a very broad-spectrum antibiotic, it's a very safe antibiotic, it's a very cheap antibiotic, it's a very well-tolerated antibiotic, and it has a huge spectrum of activity, and I would say, for 30-plus years it was not used in pregnant and lactating women because of this fear. And so it's not always the best thing to put class effects in a label. That's my only plea here. Sometimes they're relevant, and sometimes they're not.

Now, there's another issue that's come up here that I want to really be explicit about. In the 1970s, there was a court case that involved the FDA where the real question at issue was who is the expert, okay? In other words, is it external experts who are expert in the field that FDA brings in or that testify to a certain thing about a drug or a biologic or anything else? Back then there weren't many biologics. And the answer was it went to court, and it was decided, and it was appealed, and it was decided again, and it said the FDA is the expert, okay? So I don't want to say that the FDA is on the hook here, but at some level the idea of distributing information with the idea of saying you guys make of it what

you feel you should is a little bit naive because different people are going to come to different determinations about the same information for all the reasons that have been discussed here, and it's almost an abdication of the responsibility of FDA to make a learned decision or recommendation with regard to what's going on. So that's my plea about that.

Now, specifically with regard to these questions here, I'm going to go to (ii), Subpart (ii), the "interpretability and impact of animal data on decision making when there are no human data."

I will just reference something that is very important, which is there was a draft guidance document that was issued by toxicology at FDA that was a REPROTOX document in the early 2000s. That was widely read, widely circulated, and even used to some extent for a while. It was subsequently withdrawn, and the reason that it was withdrawn is because there is such a poor correlation between REPROTOX data in different animal species and what happens in human beings. It's not just a dose effect; it's not just a pharmacokinetic effect; it's a species-specific effect. There are also very, very well-known and very well-documented instances of companies that have selected animal models to do their REPROTOX studies where the species that were chosen were deliberately chosen because they are species that are known not to be susceptible to teratogenic effects. This is sad but true.

And in terms of the selection of these animal models, there's a lot of discretion on the parts of companies to choose the models. It's not complete discretion, but there's some. So this is something that needs to be taken into consideration because the correlation between these animal data that do get into labeling and what happens in humans is so poor that I would submit that it is often the case that people who read the animal data are somehow influenced by it and say, oh my goodness, this is too risky for a human.

Now, just very quickly, I'll tell you when I was in practice, people used to come to me with product labels and they would say, oh, look at this information about rat data in the label and, you know, not glibly and not without forethought, they would say, well, what does that mean to you? And I would say don't give it to your pet rat.

(Laughter.)

DR. NAHUM: Okay, yeah. And because it's not good for that, okay? Yeah, all right. Now, that's very different than what the implications are for humans, and I say that just because I want to put it in context.

The last point is, for Point Number (iii) here, when it says information that has been unhelpful with unintended consequences, I would say the inclusion of a lot of animal data in labels, I think that it can be very often misleading, and it is not really what we want.

Lastly, I want to agree, in some parts, with what Dr. Slovic said previously about -- and other people talked about testing of messaging. I would say that in the absence of being able to test every specific message, one thing that the FDA might consider is to put in place a more structured system for communicating the information.

One of the things in the current labeling of PLLR is that the degree of unstructured here is confusing to people, especially when -- and I know they're not supposed to be doing it -- comparing labels from one product to another, trying to decided whether to use Product A or Product B for a specific condition. Or if there are 15 products, looking across all of them, it's very difficult to compare things, if you're a practitioner, if the information is highly different in terms of its presentation in a different label.

And, again, going back to what Dr. Slovic said, he didn't say this and I'm not going to attribute this to him, but this is my interpretation and maybe he'll just review it with me. I think when he was talking about validity, there are two different kinds of validity. There's structure validity that can be tested, and there's content validity which also can be tested, but there's a different concept here, which is decision soundness, okay? In other words, how sound is the decision that the people reading this information, whether structured or unstructured, is? And that's the thing that we want; we want

people to make sound decisions, okay, but maybe, just maybe, we can go a long way to helping, thereby ensuring that the structure of the way what is presented is valid and that the content is valid. And I know FDA spends a lot of time ensuring content, but I'm making an argument here not to go back to the A, B, C, D, X system, but to go to a system that has more structure. And if the FDA says we already have structure in those different categories, I agree with that, but it's time for substructure. You know, substructure underneath all of those larger headings.

That's all I have to say. Thank you.

DR. BLALOCK: Thank you.

Dr. Tracy.

DR. TRACY: I'm going to go right back to that. So I'm probably going to get stoned here but -- so I just realized that I've been traveling in a couple different states, and I've been gone for a week, and tomorrow's Wednesday and I'm going to be seeing between 25 and 30 patients. Of that 25 or 30 patients, at least 3 and possibly 4 will either be pregnant or potentially pregnant. So how do I take the data that we're discussing here in these various issues -- and I do deal with quite a number of biologics now, some of which are relatively new and some of which are relatively old, and how do I communicate that? So I thought that through a little bit.

We all recognize that the baskets of A, B, C, D, and X

really doesn't work, but what I was really thinking as I've been mulling this over is really something that we use every day in my practice, and that's called a visual analog scale, where you start basically from 1 or 0 and you go to 10. I recognize that it's not perfect, and obviously, you'd have to work out the rules of how you would come up with this, much like the star system that Dr. Goldman talked about, but you can do that. I mean, you can work out your regimen, and then ultimately, you have a 0 to 10 score, but it's also a hybrid score because you also recognize that you can't communicate all the stuff that we really feel obligated to do. And so in a hybrid system which kind of deals with sort of the narrative or vignette component, I think, is kind of your next follow-on. But in the end, you know, we do have to make this -- you have to be able to operationalize this piece of information in a fairly cohesive but also concise fashion.

So I mean, we all know that there are unknowns out there, and every one of us who deal with complicated patients recognize that some patients are very highly engaged in their own care, and there's probably few people that are more engaged than an expecting mother or a potentially expecting mother and her partner. So, you know, you get past the ethical piece of shared decision making, and you come up with a system that is both clean and operational. You certainly have a 0 to 10 that kind of gives you a starting point, and then you have all the

what ifs that kind of follow.

But as we've seen, if you can't make this work in the real world, you can talk about all the theoretical stuff you want, but in the end, I'm going to work tomorrow, and I got 25 people, and I got to be able to use the data that we're discussing here. And so I kind of like the star system frankly. You know, I mean, it sounds kind of trivial, but it really isn't. So you work out the rules, you come together with something, you have sort of a grading scale, however you want to do it, and then you fill in the narrative or the vignette below it.

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: Dr. Joniak-Grant.

So Dr. Dieckmann covered my main point about rating the strength of the evidence and not leaving it up to the provider to do so. One clarifying point: We've been talking a bit about sort of looking at the evidence in combination and maybe doing a star system or something. I'm not sure if other people are proposing that they also then do sort of ratings for each sort of study underneath it, and I think that could be useful. I think then, also, if you were to do that, for example, you have animal data, and then here's our strongest piece of animal data, here's our -- you know, next and here's our next, because that -- because you have to include data, there would be something that maybe is sort of more throwaway data, and that

would be a quick way for people to look, to go in and say okay, here's the overall, here's my strongest evidence for human, here's my strongest evidence in the animal data, what does that tell me? And so that could be something that helps providers have clearer senses of what's going on with the data.

DR. BLALOCK: Dr. Winterstein.

DR. WINTERSTEIN: I just wanted to bring up one point with respect to having a gradable system or something that's discrete. There have already been a lot of comments about memorability and discretizing the information for decision making, but there's one other piece, and that's clinical decision support. Most physicians today are relying on some type of clinical computerized physician order entry that brings up flags that are warnings when patients meet certain criteria, like end-stage renal disease or whatever, and pregnancy is one of those.

Now, those clinical decision support systems cannot link to a narrative that says here's the information that we have available. They will have to link to something that is discrete. I think that this is probably -- and there's some literature on this. This is probably the most relevant source for clinical information and decision making and not the label and direct monographs, and companies that basically provide the background information for clinical decision support will have to use some system. A lot of this, as far as I know, today

still relies on that grading system. So the reality is, if there really is an aim or a goal to have information that is most relevant at the point of decision making, I think a grading system is needed unless you want to rely on something that might be developed by First Databank or Wolters Kluwer or any other of the companies that do this, because somebody will end up interpreting the information and making discrete fields out of it.

DR. BLALOCK: Dr. Berube.

DR. BERUBE: Dr. Berube. Three comments:

The first is that Dr. Yao, you seem to be basing your research on how effective the system is. I'm one of the methods editors for the *Journal of Nanoparticle Research*, which is an incredibly geeky journal, but one of the things we keep discovering is there is something called this generational nostalgia effect, and if you try to research how effective a change is too soon after the change has been done, that's what you're actually tagging into. If you wait for a period of time, the generational shifts in the sample that you're testing will eventually come to agree that the new system, which is what they grew up with, is better than the old system, which they never used before. So don't be overwhelmed by the results you're getting.

The second thing I want to say is I do spend a lot -- I write about nanomedicine more than -- in my field more than

anything, and the one thing about nanomedicine which is incredibly challenging is the next generation of nanoceuticals, which you're going to be using, have great bioavailability, they are incredibly effective. The problem is they cross the blood-placental barrier, and there's a big issue, and there's not a better time for this to be discussed because there are folks designing these drugs today. And so you're going to have to deal with this issue in the future.

I want to go off what Professor Dieckmann mentioned, and even Dr. Tracy. When I was working with big data with the NSA and when I was working with the NNI on lifecycle analysis of nanoparticles, we confronted the same issues here. It was bizarre sets of data, right, on miscellaneous animal studies. Some studies were great, some studies didn't work, and we spent an incredible amount of time trying to figure out how we would be able to provide information to folks in the toxicology world so they could try to figure out what they needed to do next, and we came up with a way to establish confidence to the datasets we had. You know, we decided that, for example, if a report -- if a study had had a finding and the finding had been cited a certain number of times favorably, then that had a better impact than one, obviously, that did not. Or if the citation the research was getting was negative, which often happens, you know, it says Jo-Jo did a study, it was bad, and they go on to talk about other things -- the animal studies

were also adjusted for this.

That's why I mentioned that logarithmic approach because what it does is assigning numbering to the quality of the data you have. And in the world of terrorism and NSA, when you're trying to predict events, what ends up happening is you have tons of data, and if you don't provide confidence levels to the sets of data you have, you never make sense out of any of this.

And so whether it's a numerical system like Paulos's logarithmic safety index or whether it's a star system or the cute little baby, you know, the number of pictures of the babies you get, these are not foolish processes; they're very powerful ways to communicate. They establish a weird sense of ecological validity in what you're doing because the data you're pulling and the data you're pushing out has special meaning to the populations that you need to reach.

Yeah, please continue to do this because you're going to have huge challenges in the next decade, and it's incredibly important that this be done properly. And I wholly support anything that comes close to confidence labeling or anything in that genre because I think what you'll be able to do is distinguish between quality of data, and that's really important to the folks who are users.

DR. BLALOCK: Thank you.

Dr. Howlett.

DR. HOWLETT: Thank you. Elizabeth Howlett.

Hey, I really think what we should be doing is actually spending our time talking about the kind of graphical systems that we could use to summarize this information. You know, I think there's a lot of agreement, I guess what I'm sensing, and one of things that Dr. Baur referred to is that there's these sub-layers. So we're talking about sort of the quality of information, and that's what I think we should be discussing. That's my first point.

My second point is I really do agree with what Dr. Nahum had said because, you know, I'm not a physician, I'm a marketing professional, and I go to a doctor, and I am depending on his expertise to guide my choice. I didn't spend, you know, X number of years in medical school, and I am going to trust him to help me interpret things that -- I mean, I'm sitting here with my computer still looking up things that you guys are dropping, like who? No, what does that mean?

And so I agree, and I think that in some sense I get the feeling that FDA is not willing to kind of put their money where their mouth is and say, hey, based on what we know, this is probably safe. I can live with that. I can live -- hey, we don't know for sure, but it's probably unsafe. And so based on human studies, it's probably not safe or it's -- so just sort of -- I mean, I just think that, you know, just as a consumer in this sense, that, you know, we just need to be able to do this in a graphic form with a little bit of, perhaps,

interpretation by some of this data.

DR. BLALOCK: And when you say graphics, are you talking about when people have suggested, you know, a star system or VAS or --

DR. HOWLETT: Well, there's a number of different things you could do. You could do, for example, you know, the quality of the data. You could use stars, you could use a bar, you could use --

DR. BLALOCK: Okay, but that really summarizes the strength --

DR. HOWLETT: Right.

DR. BLALOCK: -- of the evidence.

DR. HOWLETT: Exactly. And so if you look at the system, the A, B, C, D, X system, you know, that took a lot of information and just summarized it into one graphic. If we have multiple graphics, it's a more complex situation, but I think that, you know, we're conveying that sort of I want to look at this and, oh, it's a three-star or here's the bar. Or let's say, you know, you need a treatment for something that's going to treat MS, and so here's the risk, here's the benefits for the treatment of MS, and it's on this side of the bar. But, you know, if you're treating acne, like, you know, no one's going to die from acne. Oh, the risks are really serious if you're treating something that I would consider not to be life threatening as opposed to something like asthma or

something.

So sort of have that bar that would be saying, under these conditions, this is what you need to be thinking about, and just make it more clear cut and just put -- I just think -- well, I don't know, I'm just kind getting a little frustrated.

DR. BLALOCK: Okay, I just wanted to clarify what you were suggesting. And Dr. Yao has a response.

DR. YAO: Yeah, hi. Just in response to Dr. Howlett and Dr. Nahum's comments, just for the point of clarification. So when a drug is approved for an adult population, it has been deemed to be -- to provide substantial evidence of effectiveness and that the risk-benefit has been -- has been decided to be acceptable for all adults, and that includes women. So the probably safe bar has already been met for all women, including pregnant women, unless we have any understanding that there is a clear contraindication and that's when we put it in. Sometimes we would like to have more information on the more specific dosing and safety in pregnant women, and we don't get that at the time of approval, but I do want to make sure that that's clear before we launch into, you know -- I have heard clearly that, you know, FDA should be, you know, more clear in this description. I also want to make one other point, just for clarification, and that is FDA is required, as I described in the session yesterday, what is required in labeling. But the other thing that needs to be

clear is that FDA does not and is not -- cannot regulate the practice of medicine. So we have to be clear that we can't stray too far into what would be considered practice of medicine.

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thank you so much. First, I want to say that, you know, I truly appreciate the passion of Dr. Robotti and Dr. Goldman, and I think we all want what's best for our patients, and we all want to be able to have that evidence to be able to tell women and tell families what is best for them, and I don't want anyone to think that this Committee doesn't want to do that and doesn't want to give them the best information that we can. The difficulty we have, of course, is we don't have the best information, and although I would love to say that this Committee also is charged with that, it is not. But I think, you know, I feel your passion; I have that passion as well, and I would love to have additional information, and you know, I think many of us are working as hard as we can to try to get that information. So I just want to make that very clear that, you know, I think we're all in agreement with you that that information would be helpful.

I think, specifically, to this question of how effective has it been in conveying the evidence, I think yesterday there were some examples of how perhaps we could tweak this system, and I just want to make a couple of suggestions. As far as the

animal data and whether it should be included, I'll admit, I thought that any data we had, had to be included. So to me it was yes, it has to be included because it's required to be included. I think it would be incredibly helpful though to provide, in that animal data, a little bit of, you know, what does -- how would you translate that, then, to humans, right? So, you know, third trimester in a rat or in a mouse is neonatal, right? So what does it mean if you were treated -- if you had given 25 times the dose of a medication to a pregnant rat and they got this? You know, putting that into some context would probably be helpful for providers and practitioners.

I think that this idea of having each document consistent in format would be very, very helpful and make certain that in those subheadings that were described, if we don't have information, there isn't information, but it's not that it was omitted. So does it cross the placental barrier? We may or may not know, but just say unknown or say what's known. Does it cross the placenta; does it cross breast milk? You know, having that information in the label, I think, would be helpful. Having a label that is consistent would be helpful.

And I have just two other additional points. One is that, as was discussed a little bit yesterday and I think is something very important, this label would be very helpful if the mechanism in which people accessed it, given that the next

generation does everything electronically, to have it so that it is easy for them to come up with, you know, what are the take-home points from this label, how do they get to those points, I think, would be very, very helpful for them to use the label more frequently than is currently being used. So having it in some way really able to be pulled up on a phone, able to be pulled up at point of care, to know what it says in a very fast manner, I think, would be something to consider.

Although I would love it that we could reduce the label to include a scale, I'm not certain that at this point, given the information we currently have, we can do that. Even a complex scale that we've got, you know, a line for animals, a line for breast milk, a line for the placenta, etc., I think, as we get more data, maybe we can move towards that, but I don't know that we're at that point yet.

Thank you very much.

DR. BLALOCK: Dr. Coombs.

DR. COOMBS: I'd like to go back to something Gary brought up, and that's the notion of requisite variety, because I think that's what we're seeing, particularly with 2 here, is the notion that sometimes you're in a much more complex environment, and requisite variety says, when I'm in a more complex environment, I have to be more complex in how I deal with that environment, and I think that's what these new guidelines which are coming are trying to do that. When you're

in a more complex environment, how do we do that?

But then you get the types of comments like you had from some of the physicians. They view the narrative as long and difficult to understand. Anyone in education has heard that repeatedly from every student that comes through. Oh, I had to read the book. Oh, I had to read the article.

So I think one of the things we can do, and a number of the comments that were brought, is to perhaps -- the label can only be so big, but behind the label there's some guidance to help kind of further clarify what that means and to help them then explain that when they then talk with their patients. Again, I'm not trying to get into what they should do with their patients but just how they might talk about it. That guidance behind might help them because, in education, that's what we have to do all the time, is to kind of backload some of that notion in for our students so they can better understand it.

DR. BLALOCK: Dr. Lyerly.

DR. LYERLY: Just a couple of points. First, I wanted to agree with Dr. Dieckmann and his idea of developing some measure of the quality of evidence. I know, particularly for OB/GYNs who move fast, when ACOG develops guidance, at the end of every guidance there is a level of evidence for every recommendation. I also think here, though -- and in some ways I think it goes without saying in this room, but I'm not sure

that I've heard it said, is that magnitude is really important here. So if you have very high-quality evidence that cleft palate is increased, has a relative risk of 2, that's still a very low risk of a cleft palate, right? It's like 0.6 in 10,000 pregnancies moving up to 1.2 in 10,000. So, again, if you're thinking about a patient who is thinking about a treatment for their disease, that still may be, even if there's very strong evidence, something that they should consider taking. So I think important in sort of this schematic is a magnitude question.

Also, I think when I have looked at the summaries here, there is a variable mentioned of trimester, and I know that from case reports that I've studied that there's a tendency to not pay attention to trimester when interpreting safety signals. So if there's a risk of a neural tube defect from taking a medication, then that gets off the table for the entire pregnancy. Public health problem programs are changed because of that. And so it seems to me that in the schematic it would be very important, not just even for the animal data but for any data, to have some specificity with regard to trimester because, you know, not everybody who prescribes these remembers their embryology classes, remembers when different organs are formed.

Finally, I just want to go back to this sort of approved for adults and probably safe bar has been met, because I just

do not think that doctors know that, and I think it's just worth discussing whether there is a role for that kind of statement in the label that says FDA has approved this for adult populations and that includes pregnant populations. I mean, not specifically for the condition of pregnancies, but pregnant women are included in adult populations. That is something I have heard in my conversations with FDA, I have read in the depths of papers written by FDA people, but I do not think that is something that doctors know and prescribers know.

Okay, that's it.

DR. BLALOCK: Dr. Cappella.

DR. CAPPELLA: So I'm very much in agreement with the tenor of the conversation that I think was begun to some extent by Professor Dieckmann, essentially saying that the core issue that is the most difficult one from the point of view of communication is communicating the uncertainty and that uncertainty is attached to the kinds of evidence that are present. And so some of the conversation has been, you know, star system, numerical system, and so on.

One of the things, one of the systems that I found particularly useful is something that's come out of the National Academy of Sciences, Engineering, and Medicine on evidence-based conclusions about particular kinds of tobacco products, and they developed a six-level system from no

available evidence, insufficient evidence, limited evidence, moderate evidence, substantial evidence, and conclusive evidence, along with a two-, three-sentence summary of what each of those evidence bases are. And I can forward that to you, but just to read you, as an example of the moderate evidence one, and then I will shut up and not read the others.

There are several -- for moderate -- uh-oh, it just disappeared on me. Don't go away. For moderate evidence, there are several supportive findings from fair-quality studies with few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable evidence. So the language here, I think, is simple. It's clear, it's talking about evidence, it can be -- keep the word "evidence" or not, but conclusive, substantial, moderate, limited, insufficient, not available, and that provides a clear and unequivocal way -- not unequivocal, a clear way of describing the evidence base. A judgment would have to be made by experts, but that's been done before. And then you can still provide the evidence if you wanted to, but people wouldn't necessarily have to jump to that evidence. Anyway, I thought that's pretty useful.

And then in each of the conclusions that they were reaching about particular elements in, in this case, e-cigarette case, each conclusion had attached to it various

substantial evidence, that there is moderate evidence. I found that useful.

DR. BLALOCK: Thank you.

Dr. Baur.

DR. BAUR: So Cynthia Baur.

I'd like to gently disagree with Drs. Howlett and Nahum and extend what Dr. Yao said about FDA's role in these PLLRs, because I think that they can do a great public service by bringing transparency to this process of conveying safety evidence and being circumspect on this question of recommendations, because I think there's a very large issue of reputational risk to FDA, as an agency, to go down that -- too far down that path of recommendations.

And I think we've been discussing how much work there is to be done just on conveying safety of the evidence. And I think this issue of transparency, which I think has been a subtext to the 2 days, really goes to the fact that what you're trying to do is represent what industry has told you, what experts have told you, and what your own internal analysis has told you, and to synthesize that in some way in this PLLR to convey the safety of the evidence.

And so I would just encourage you to stay on that path and to be a little bit cautious about going down -- going too far toward a recommendation because I think that could be pretty fraught for you. And I think the public service is really in

the transparency around this, is how we've learned what we know about these drugs, and this is what we're doing to share that information with you so that you can use it however you need to use it to make a decision.

DR. BLALOCK: Thank you.

Dr. Slovic.

DR. SLOVIC: I just want to comment a bit on the animal data and the concerns that Dr. Nahum raised about that. I'm probably the only person who's done systematic research on how toxicologists and lay people interpret data about something like carcinogenicity of exposures to some chemical. Working with toxicologists, we coined a subdiscipline of psychology called intuitive toxicology to contrast the way a layperson reacts to information about toxicological evidence and the way the toxicologists react to it, and as you know, a major process that toxicology relies on is animal testing. Let's say, for carcinogenicity, they test animals at very high doses for long periods of time. It's a very conservative type of process designed not to miss problems. It's biased in that way, and it's very conservative.

What we found in these studies was that the concept of a dose-response relationship to a carcinogen, which is so central to evaluating toxicological data, was pretty much missing in the layperson. They believed that if something, a chemical, caused cancer at high doses in animals, it was likely to cause

cancer in humans at low doses. Toxicologists recognized that that was not the case, and they're much more cautious in -- you know, in their interpretation of that evidence, but they never communicated that to the public.

Thousands and thousands of animal studies have been done, providing a large database often with findings of carcinogenicity that led people to -- some people call it chemophobia because the toxicologists did not play a role in interpreting to the public the limitations that they knew about of those tests. They just did the tests and put it out there, assuming that the public could interpret that.

So I think that one would have to expect that if there is animal data listed in the labeling that shows evidence of harm in animals, that if people or their providers see that information, they're going to give that very heavy weight, especially in light of what Dr. Nahum mentioned about the problem of omission versus commission, you know, that people are loath to prescribe something that they think might be harmful, and they're likely to think that the animal data is relevant to humans, and their patients are likely to think that as well. I just want to put that out. I don't know exactly what the implications are for how animal data is presented or relied on in these labels, but that's likely to be a way that both providers and their patients will interpret this data.

DR. BLALOCK: Thank you, Dr. Slovic. And I think that

will be relevant, you know, to the fourth question that we have to address as well.

Two more folks are on my list, and then we will kind of -- I'll close this up and we'll take a break. Dr. Nahum is first, and then Dr. Goldman.

DR. NAHUM: Thank you. Dr. Nahum.

I think you'll happily see, Dr. Blalock, I'm moving on to the next set of questions in Number 2, which is 2B, because that really hasn't been explicitly addressed, but this is about observational study data of various sorts. I don't know if you want to advance that slide or not, to show that. But I have several comments about this, and one is Subpart (iii), which says observational study data where there are methodologic limitations, my comment about that is that all observational data have methodologic limitations. Okay, so I don't interpret this as being specific only to this subpart. I believe that the methodologic limitations apply both to Subpart (i) and to Subpart (ii), and I want to just say that explicitly.

Observational data is not well-controlled data most of the time. One can, you know, do case-control studies with it, one can do perhaps, cohort studies with it, one can even do longitudinal cohort studies with it, but this is not the same as very well-controlled, certainly not randomized data, and there are all sorts of biases that creep into this data, as well as confounders that may or may not be able to be

controlled for.

As far as the idea of visual presentation of data, and I think this has been brought up several times, I think there's a good example, and Dr. Nguyen will know very well about this. In the Bone, Reproductive, and Urologic Division, DRSP, which is a progestin, was very, very closely evaluated, not just by FDA but also by European agencies back a decade ago, and the contention was that there was perhaps, and it was unproven, a relative risk increase with regard to thromboembolic events, which most literature did not conform to. However, there was some literature that did suggest that from some databases in some countries in some settings, and ultimately what made it into the labeling -- and this is the reason I'm bringing it up -- was something that I think is very, very effective at communicating what the level of human knowledge was with regard to this. And it was a forest plot, and I think most people are familiar with what that is, but that's where all of the studies that were considered to be informative and had sufficient quality for FDA to include were plotted so that there was a relative risk associated with it either being over or under other controls. And we could argue for a long time what the proper controls should be, but we're not going to do that here.

But what the forest plot does is it outlines all relevant studies. It says, effectively, how big, what the size of the study was, by the size of the marker on the point estimate, and

it also gives confidence intervals. So you can look down a forest plot, see all the information that's relevant to a particular issue, and then make your own judgment based on that information. And sometimes there's a meta-analysis of one sort or another that's performed, also, to try and combine all the information.

And by the way, Cochrane and the Cochrane databases are very good at trying to summarize information in this sort of way. So there's a model for this.

The one thing it does not address, and that the FDA would still have to weigh in on, implicitly if not explicitly, is what should be included. In other words, what's the quality of these studies? What sort of level of attention to data collection and data cleaning and data interpretation was given in the various studies? But that's something that I think we need to give back to FDA.

The other thing I want to bring up with regard to this point is the idea, and it's been brought up before by several people, about biologic plausibility. You know, this is not new. Causal assessments have to rely on some sort of mechanism, and it's not new because Sir Bradford Hill in the 1960s came up with a compendium of nine criteria for how to come up with a causal relationship instead of an association, so this goes back more than 50 years. And one of them is this idea about plausibility, is there a mechanism.

And what I get to here is I think it's critically important that included in these labels be two pieces of information, if available, and it should be mostly available, which is does the molecule or biologic involved cross from the maternal circulation into the fetal circulation across the placental barrier? There are very well-known instances of macrolide antibiotics, for instance, where the penetration of the fetal compartment is essentially nil, and it's very difficult to come up with a mechanism whereby there could be teratogenicity or fetal harm, you know, absent a much bigger problem of a fetal internal shunt or something like that, which in that case it could happen, but that's a much bigger pregnancy-related problem than anything having to do with the macrolide antibiotic.

And the second point is does it cross into breast milk? And that's often much more easy to determine because you can collect breast milk pretty easily. And if so, how much? You know, this gets to the idea of there being thresholds and possible, you know, biologic plausibility to newborns being exposed.

So I would vote for there being some sort of a causal assessment being made in terms of labeling, and the way that you can do that in these two instances is say does it cross into those places at all, because if it doesn't, it shouldn't really be very much of a concern.

Thank you.

DR. BLALOCK: Thank you.

And Dr. Goldman.

DR. GOLDMAN: Okay, so three things: One is I agree, and I wanted to circle back with Dr. Lyerly's point that I've heard several Committee members comment on, that they didn't sort of appreciate concretely that pregnant women were included as a subpopulation. And so to tie in with what Dr. Pleasant said about metadata, like I think an actual discrete statement related to that would be valuable.

And then the other thing is at some point you asked do we want confidence intervals, and the answer from me is yes, and I just want to make sure to answer that because I wrote down a note that I like to look at that because that's sort of the highest potential risk, and we deal with that with PML, you know, all the time and the drugs that I treat, so that's very valuable.

And then the last thing is to come back to Dr. Spong's comment about the electronic, right, the upcoming generation. And so to make the things -- and for some reason, I was trying to get on to the website to play with it, because I confess, I don't go specifically to the FDA to get the package insert when I read it. I will now, although I noticed you went to DailyMed yesterday, which is an NIH website. So like we're not even using your website, as far as I can tell. But anyway, I

digress.

What I wanted to say is that you should embed links to the papers so that if I want to like come back to Dr. Coombs's comment about varying -- so if I want to go read the original animal data because I am thinking through this decision, it's very easy for me to get to it. So in the references -- or somehow to make those PubMed links. Like I think we should just -- I would encourage you to brainstorm about not just sort of the content, but the usability of this as we think about it for generations to come.

DR. BLALOCK: Okay, Dr. Spong for a very quick final question.

DR. SPONG: So I just want to come back very quickly to the concept of trying to say risk with one graphic, and I think one of the difficulties we have is risk, as we look at it, is very different, and even with a forest plot to say, okay, well, the risk for a clot would be this. You know, you've got risk for miscarriage; you've got risk for, say, anencephaly, which is clearly severe; you've got risk for polydactyly, which perhaps is not nearly as severe. Yes, those are both malformations, but they're very, very different. And so having one single risk, I think, is problematic.

DR. GOLDMAN: But we could have a forest plot of the strength of the data.

(Off microphone comment.)

DR. GOLDMAN: No, no, no. I mean the overarching, like three or four things, like human data, you know, animal data. Like that's sort of my idea. It's just to say --

DR. SPONG: Right. So I guess the question is what is the risk? If you're looking at --

DR. GOLDMAN: Not risk, but what is the amount of -- what is the amount of light that is shining into this dark room? And then --

DR. SPONG: It was the amount of data we have available.

DR. GOLDMAN: Correct.

DR. SPONG: But it's still --

DR. GOLDMAN: And the quality of it.

DR. SPONG: -- the amount of data to show that it is polydactyly doesn't probably matter to me.

DR. GOLDMAN: But that's for the FDA to -- right. I mean, that's for the practitioner to decide.

DR. SPONG: As long as they knew that polydactyly was the endpoint there, right?

DR. GOLDMAN: Right.

DR. SPONG: If you're just showing a forest of what good data we have or don't have, it depends on what that good data is on. And so it just gets --

DR. GOLDMAN: Yeah.

DR. SPONG: -- really complex.

DR. GOLDMAN: Yeah.

DR. BLALOCK: Okay, I think I understand, and I think that your concern is --

DR. GOLDMAN: I think we should forego a break and just keep --

DR. BLALOCK: Yeah.

DR. GOLDMAN: No, I was just kidding.

(Laughter.)

DR. BLALOCK: We're probably on the verge of driving the transcriptionist crazy with folks talking over one another. But I think what the issue is, is that once there become multiple risks, it becomes complex, even if you're talking about the probability of the risk or if you're talking about the strength of the evidence with respect to that risk. So let --

(Off microphone comment.)

DR. BLALOCK: Okay, Dr. Yao.

DR. YAO: Just a clarification to Dr. Nahum's point about bullet (iii), sub (iii). So we understood that all observational data have methodological limitations. The point of that question, for clarification, is that when -- at what level of limitation is just too limited to even consider including.

DR. BLALOCK: Thank you. And, you know, this is a wonderful discussion, and I hope that you're getting, you know, useful information and the kind of feedback that you wanted.

I'm just going to summarize very briefly and bring Question 2 to a close.

You know, I'm going to go back to what Dr. Baur said at the very beginning, which I actually think -- and it wasn't picked up, I don't think, by very many people, but I do think it is worth considering, and that's thinking about this as safety communication. You know, rather than risk communication, you know, the opposite of framing that is safety communication, and you know, that's probably no easier to do than risk communication. But as you're thinking about it, think about what the implications of that are, and are we clear when the drug is risky, are we clear when it's safe, are we doing that clearly?

The issue that I think I heard come up most consistently across the members of the Committee, you know, was a need for sort of greater consistency where that's possible. And I know that I've heard from the FDA that, you know, often things get complex very quickly, and you want to start out by having 4 buckets, and all of a sudden you end up with 40 buckets. But to the extent that there can be greater structure within the structure that's already provided, and consistency in the languages, then as a user, they're going to know what to expect and know better how to interpret that.

There was a lot of endorsement of the idea, I think, that Dr. Dieckmann initially proposed, was some kind of a way of

conveying not what the risk is, but what the strength of the evidence is. You know, whether you're talking about risk or safety, how much evidence is that based on. And I think that's actually relevant to the last discussion that we got into, that it becomes complex when there is multiple risks going on. But I think that's probably why people like the letter system, because it's summarized, but it did kind of confound risk versus the strength of the evidence, and what Dr. Dieckmann, you know, said better than I am, is that, you know, some kind of way of communicating, you know, how much evidence is this final judgment made on, whether it's a verbal descriptor, whether it's a star system, whether it's a visual analog or something else.

I'm going to stop there. You know, at the end, at the very end, everyone's going to -- we'll go around the table, and everyone will have an opportunity to say, you know, this is the most important thing that I think -- that I think you guys should think about, the FDA should think about.

So let's take -- I've got 22 after, so let's call it 11:30. And do come back promptly at 11:30, and we're going to probably reconfigure the rest of the schedule a little bit, in light of our time constraints.

Thank you all very much.

(Off the record at 11:22 a.m.)

(On the record at 11:31 a.m.)

DR. BLALOCK: Let me call everyone back together again, so resuming the meeting. And we are -- you know, we're looking at the schedule and then kind of reconfiguring a little bit because we are running, you know, a fair amount behind, and we don't want to cut off the conversation and the discussion too much. And I really think that this is a really valuable meeting, and the FDA should be getting good feedback.

So, with that in mind, we're anticipating that we might run a little bit long, and we polled all the parties together. We might go as late as 10 to 1:00, so 20 minutes long. All of the taxis ready to sweep us to the airport are standing by. They've checked for Dr. Sneed, and that should not be a problem as long as we do promptly at 10 to 1:00. I'm going to end promptly at 10 to 1:00, and everyone needs to be ready to, you know, pack up their bags and get out the door and get to the taxi cabs at that time, the shuttle.

So let's go ahead and get started, and we are at Question 3. So 3A. I'll let folks look at that and read it for yourself.

DR. BAUR: Are these defined in the PLLR? Is "adverse developmental outcome" defined in some fashion? And similarly, is "limited data" defined in some fashion? We could get what the adverse developmental outcome --

DR. PLEASANT: Just quickly, add a glossary.

DR. BLALOCK: And, Dr. Yao, you're checking on the

definitions? Okay. And the reason I was looking down, there are actually three parts to Question 3, and I think that, you know, we can discuss all three parts at the same time. You know, the first part is really, you know, the language and these terms, and Part B is discuss how language affects physician willingness to treat patients, patient decision making, pregnancy planning and prevention. And then Part C is "Discuss intended and unintended consequences, including prescriber liability, that may occur with certain language or communication approaches." So the focus in Question 3 is on the specific language that's being used, but with that in mind, I think that we can take on all three parts at the same time.

So, Dr. Yao, did you find that?

DR. YAO: I did, and I can send it as a slide or whatever, but adverse developmental outcomes include the following four groups of developmental toxicities: structural abnormalities, which describes dysmorphology; embryo, fetal, or infant mortality, which is obviously mortality, stillbirth, miscarriage; functional impairment, so that would be something like neurodevelopmental deafness, etc.; and then alterations in growth, so growth restriction, excessive growth, delayed/early maturation. So those are the four general categories of adverse developmental outcomes.

DR. BAUR: And are they further broken down when you talk about the risk or the chance by those four, or it's just in a

lump?

DR. YAO: And just for clarification, we have in general. Unless we've had specific information to describe a specific adverse, we talk about them as the overall group of adverse developmental outcomes.

DR. SPONG: Are you ready for comment? Thanks. So a couple of things. One, lumping all that together, to me, is problematic, because again, very, very different. Death is different than a small baby or a large baby or a structural birth defect. So, to me, it would be preferable, as a clinician, to be able to parse that out and say, you know, this is what that risk is; the risk is small for gestational age or the risk is stillbirth or the risk -- and to know the quality of that data as related to that risk. I think it would be helpful to say what "limited data" means, and I appreciate that it's hard to define that, but however you're using that term, we probably should have a definition for that.

I think one of the key points that really hasn't been brought up yet, that has been discussed to some degree and is included here in this communication, is the fact that conditions that women have, have different rates of these risks already, right? So your risk of miscarriage if you have diabetes or if you have lupus is different than if you have asthma. And so if you're on a certain medication, it depends on what the underlying condition is to know what that baseline

risk is; more than just the 3% risk of anomalies, right, there's all kinds of other risks. And so recognizing that complexity, I think, goes back further into this communication with these words, as well as into the idea of a scale.

DR. BLALOCK: Dr. Sneed.

DR. SNEED: This has come up several times over the last day and a half, but use of plain language is very important. Use of consistent terms. Number 3 and Number 4, I think both could be said in a more clear manner. And so looking at ways that, you know, have not -- "data have not reported a clear association." Data don't report anything. So think about just in plain English what that says to people.

DR. BLALOCK: Dr. Berube.

(Off microphone response.)

DR. BLALOCK: Dr. Pleasant.

DR. PLEASANT: Thank you, and thanks again, Michael, for replacing my microphone.

Specificity is one way to successfully navigate complexity and a lack of information. Categorical labels like this tend to work against specificity. I think that's kind of what Dr. Spong was trying to get to as well. So I'm not a fan of any of these. Just to pick on one, "available data are not sufficient to inform the risk," it's not the risk that's being informed; it's the decision about the risk or the benefits. I know that within science we'll talk about informing the risk,

but we're not. The risk is the risk. People are informed. And I do find it interesting that you, on B, Part (ii), go back to patient decision making and adherence despite the earlier strong statement that this isn't about people, it's about the healthcare providers, but we're ultimately going to have embrace the fact that shared decision making and empowerment of people, as healthcare seekers, is going to have to be the answer to this.

And then on 3C, I don't believe you can talk about any of those consequences if there is no data to indicate that they're there. So that, again, is your biggest limitation, and I go back to specificity and language and say exactly what the evidence says. And whether it's a healthy baby, a graph, or a letter -- A, B, C, or D -- you're still using a method of simplification, which is going to cloud the actual evidence that's there.

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: I would like to stress that with patient decision making, that if we're talking about shared decision making, that it actually is a shared decision. I'm finding, as more data comes out that's unclear or language is slanted in the negative, for example, saying "available data have not reported a clear association," which sort of gives the idea that there may be an association or they're on their way to the association, that some healthcare providers are backing

away from making decisions or giving information. I know plenty of people that have said, well, if you were in my shoes, what would you do? And they get shrugs and responses, or I don't know what to tell you, you have to decide.

And so we need to be mindful, too, that as the data is -- you know, the more unclear it is, the more some practitioners are just backing away from it altogether and saying you've got to decide what you're going to do, which as a patient who hasn't had years of medical training is a really terrible position to be in.

DR. BLALOCK: I actually have no one on my list with additional -- oh, Dr. Dieckmann. Oh, okay. Dr. Dieckmann.

DR. DIECKMANN: Nathan Dieckmann.

So I think some of the discussion about the specific words here will probably have to wait until you decide, if you decide, on another scheme for representing the strength of the evidence or quality of the evidence, because whatever scheme you choose will probably have some words that will be more consistent across -- because some of these here -- I guess I'd also say, so beyond going and looking at these individually and picking them apart, I'd say that first.

The other part, I think, to be clear on is to try to separate out the strength of the evidence and the statement about that and then the claim about the hazard itself. So if you have information about the probability of a particular

hazard, you can claim that or you can say that. Then, along with that, you'd have some claim about the strength of the evidence that's underlying that.

So I've seen in some of these, as I've been reading through them, I feel that sometimes kind of like with the original pregnancy categories, those things are kind of combined together, both the probability of the hazard and the strength of the evidence, in a single statement, which I think can be confusing even to me, and I study this stuff all the time, trying to separate these things out. So I can imagine, to a prescriber or a layperson, it would be pretty confusing to parse. So I would just try to clearly separate those in whatever scheme that you choose.

DR. BLALOCK: One thing that I also wanted to mention in relation to this question, even though you don't ask about, you know, the format of information, I was sort of surprised in reading the guidelines that, you know, there's a lot of recommendations and, in some cases, rules about the content that has to be presented and often, you know, even whether things had to be in a subheader and italicized and things like that, but there -- I did not see any recommendations in relation to presenting things as absolute risk versus relative risk versus odds ratios, and at least in one of the examples there was, in the data, information presented as relative risk. So I'm not going to make any comments related to that, but I

think this is the closest in the questions that approaches, you know, sort of the format and if we have recommendations to make regarding how things should be formatted.

Dr. Baur.

DR. BAUR: So Cynthia Baur. I want to address 3B, under patient decision making, adherence of treatment, and pregnancy planning and prevention.

So what we know from research is that when people don't understand things, they end up, you know, misinformed or filling in the blanks with what they already know or, you know, deferring the decision. I mean, there's sort of lots of negative consequences when people don't understand things.

So I think that also links in to C. I kind of interpret it differently, I guess, than Dr. Pleasant had. I think the intended and unintended consequences are that if we use communication approaches that rely on like passive voice writing, which a lot of the current labels do, we have a lot of evidence that people don't understand passive voice construction very well. They don't know who the actor or the agent is. And so this goes back to my prior comment about this process bringing transparency to where the data come from, what research actually means. This goes to the comments that Dr. Dieckmann and others have made about the quality of the evidence.

So I think these things are all connected in that we

continue to kind of perpetuate the black box or the behind the curtain that Dr. Goldman referred to, or the dark room, because people will not have any better understanding of the research process and where these data come from. So a statement like "available data are not sufficient to inform the risk," I mean, there's just all kinds of ambiguity there, what available data, where did these data come from, what does sufficient mean? You know, inform, as Dr. Pleasant said, the decision, not so much the risk. So I think any one of these statements is just kind of rife with ambiguity.

So my concluding comment, though, is to loop back to the question about testing, and I think one of the most valuable things this Committee and other committees could do is support the FDA and other federal agencies in this end user testing, because there is a very specific reason, in addition to budget, why agencies don't do more testing, and that's because agencies are subject to the way the Office of Management and Budget interprets the Paperwork Reduction Act. And so if this Committee and other committees were to make the point that the Paperwork Reduction Act really is not applicable to the kind of end user testing that we're talking about, we would be doing an enormous public service.

DR. BLALOCK: Dr. Tracy.

DR. TRACY: I guess this really comes under B, but I just want to talk a little bit about the language here, first about

the outcome. You know, I think a lot of the discussion is sort of at the provider level. I think it's -- you know, in our world of the internet, it's equally confusing to patients, and we're often talking about mom, but also something that I've seen is the dads get confused, too.

So a very common scenario might be that somebody is -- I'll go with my area of expertise, which is asthma. So they have moderate to severe asthma, they're pretty well controlled under the medicine, I may only see them a couple times a year; they get pregnant in the interval, and they stop their medicine because "I'm going to stop all my medicine because that's what you do when you're pregnant." And they come in, and maybe they're unstable, maybe they're stable, whatever the reason, but they stop and now -- and then as the cases go in this, is sometimes they crash and burn, and sometimes they just kind of fizzle, but a lot of times they would -- in almost every case they would do better if they were still on it. So then I see them in my office, and I say, okay, you know, this is why you should do it, and we'll go through the risk-benefit talk, and they'll go home and say, okay, Dr. Tracy, thank you very much, and I'll start taking my medicine. Then they go home, and they talk to a spouse, and they'll say, "Mary, are you sure you really need that medicine?" And so they'll know it's filled with self-doubt, and a lot of times they'll have gone back to some of the stuff that we're reading about, limited evidence or

the like, and they'll say, "Well, you know, nobody really knows the answer to that question." I don't know how we address that, other than in the human interaction at the bedside, but that is -- it's not just limited to the providers here; it's the patients and their families too. I guess I'll save my next --

DR. BLALOCK: Dr. Nahum.

DR. NAHUM: Thank you. Gerard Nahum.

I have two points here, and if you can go back one slide because it was 3A that I wanted to talk about a little bit. So this one is point to the "limited data" piece. I would submit, and I think everybody would probably agree, that data is always limited; we never have it all, right? So, to my mind, data is either sufficient to make a particular determination or judgment, or deficient or insufficient. And, of course, that depends on who's analyzing it, for what purpose, under what sort of system of analysis, and you know, those are determinations that the FDA would have to make in terms of sufficiency or insufficiency. But I don't like the term "limited data" because it applies to all circumstances always. So I don't really know what that means.

And my second point is -- and I think Dr. Blalock was alluding to this before. One of the things about this question of risk that keeps coming up and that we've discussed -- and Dr. Slovic has pointed out some very important things about, I

would like to make the following suggestion, that there are four kinds of risk, but there's really one kind of risk that anybody's terribly interested in as a patient. And there's a baseline risk, which is population based; there's a disease-specific risk that is specific to a particular class of people within that population, that particular, you know, disease, and there may be a spectrum associated with that, that's associated with the severity of the disease. And then there's a medication-specific risk, and that's what people are interested in here. But when you compare, you know, the second and the third one, it comes down to what I would call an excess risk, and that's usually referred to as an attributable risk to the medication.

And I think that's what people are interested in, to frame things in the idea or in the mindset of what is the excess risk. Then you can sort of put that in relative risk terms or hazard ratio terms or odds ratio terms, but that's kind of the crux of what people and practitioners and plaintiffs' attorneys want to know. You know, I say that last thing tongue in cheek, but I think it's actually true.

So I'd like to make a plea that those kinds of information be incorporated into labeling of this sort routinely because I think that's what really the issue is here.

Thank you.

DR. BLALOCK: Dr. Lee.

DR. LEE: So I'm going to combine the response from 3A to 3B, Item (i), and reinforce what Dr. Sneed said about use of plain language. And when I was looking at this from a perspective of a prescribing physician, I was thinking under what situation would I recommend treatment if I saw this? And when I was looking at this, it occurred to me, this is from very scary to least scary, and I think the fourth one is probably the best option, but I'm not exactly clear. And if that is the case, you know, can you go from being less scary to being reassuring? I mean, is that possible for the FDA to do to convert the fourth one to say there is no increased risk or something like that, rather than saying there is no clear association?

DR. BLALOCK: Dr. Yao.

DR. YAO: So just a clarification. These statements were not intended to be sort of in a spectrum of more scary to less scary. They're statements that we're using, and we're using them in different situations, and we wanted -- and admittedly, it's hard to get the context because we're pulling these out of the paragraphs that they appear. The way that the comments are being received, anyway, what you're providing us is very helpful, so we'd have you keep going on. We just want to get a flavor for what is helpful about these statements or actually unhelpful.

So in terms of to answer your question, Dr. Lee, we do

have -- I think we showed it yesterday with the -- it might've been the -- I can't remember with the -- it might've been the Herceptin example, but we have -- when we have data that we're sure that it shows something or we're confident that, you know, it doesn't show something, which is again harder to prove -- oh, with the HIV, the HIV drugs. That's in your backgrounder. We have statements that are a little bit stronger than this. These statements tend to appear in that space of uncertainty that we've been focusing on this morning.

DR. LEE: Yeah, to follow up on that, I think your goal is to increase potential recommendation of therapy, and if all of these are not -- that the physicians don't recommend, I don't think the differentiation results in the action that you're looking for.

DR. YAO: Lynne Yao. I just want a clarification there, too, because I was hearing -- I think all of the comments are really right on, but part of our problem is, you know, this description of what is the outcome or what is the probability or the chance, and then what is the strength of the evidence. So, oftentimes, we're dealing with -- and I want folks, maybe the Committee, to consider this as well. So we understand that it's not necessarily very clear, and it may sway people to not prescribe when it says, "available data have not reported a clear association." But a lot of times when we're faced with the data, we get something that is, you know, 20 case reports,

two of which showed a cleft palate, one of which showed a VSD, and another -- and eight that showed nothing or something like that. And so, you know, we feel like reporting on all of that may actually lead people to be more scared, so we're trying to say, okay, what we have doesn't -- is nothing clear, and when we say limited, it's, you know, again, we have not been clear about that metadata piece, or what do we mean when we mean limited. But that's sort of where we sit, and we'd like some advice on how to be more clear when that's the situation, because that's usually the situation.

DR. NGUYEN: And I'd like to add, if all of these phrases convey a certain interpretation, like you say, if they're all scary from a prescriber's perspective, we would like to hear that. And then the second part is if you have different ways of phrasing this in a way that's a little more balanced, we would welcome those suggestions.

DR. BLALOCK: And that was Dr. Nguyen.

Let me summarize what I've heard so far, at least the things that have sort of resonated with me. You know, to start out with, Dr. -- I think it was Spong, I'm not exactly sure, had asked a question for the definition of adverse developmental outcomes and noted that, boy, there's an awful lot of stuff in there, and maybe they need to un-package that into more descriptive terms, and my sense was that the things that are comprised in that umbrella, some are scarier than

others.

Okay. The second issue, again, that I've heard is that really 2, 3, and 4 are all problematic, that, you know, what's limited and I guess your suggestions, a suggestion from Dr. Nahum on replacing that with something close to sufficient or not sufficient.

And the terms "available data are not sufficient to inform risk," "available data have not reported a clear association," you know, I am virtually certain that if you got 10 clinicians in here, you know, without experience in this area, that they would interpret those phrases in 10 different ways. And folks can have a chance to disagree with that. So, you know, I think -- so what I heard others say was that those, you know, 3 and 4, you know, they're just ambiguous. And I'll stop at that and go back to my list.

DR. GOLDMAN: Can I ask a point of what -- yeah, that was --

DR. BLALOCK: Oh, actually you're next. Sorry.

DR. GOLDMAN: Okay, that was going to be my point of order. I mean, I think we have a lot of people that have things they want to say, and we have a very limited amount of time, and I'm not sure, like re-contextualizing what's been said, is I don't know the best use, but just for putting that out there.

So two things: I think, in terms of language, you know,

based on the papers that I read, and there's experts in this room, but I think one of the things that might be helpful is to say, "available data has not identified a clear association." So "identified" feels a little bit more reassuring to me than "reported." And then also keying off of the language documents that were given of the good article written by one of our guest speakers, "available data are not sufficient to inform the chance of a bad outcome," rather than risk.

So, again, I think what we can help contribute to here is specifically this is the language that they're currently using. How can we take this language and shape it in a way that would be helpful? And so just to, you know, sort of make the point about Point (iii), which is pregnancy planning and prevention. So there are two drugs that we use: One is a Category X, which is otherwise very safe, and the others are Category C, which is safer in terms of pregnancy but is associated with a fatal brain infection. And in my practice in neurology, doctors are widely refusing to give the Category X medication to any woman of childbearing age. So she has a uterus, she can't get the safer medication, and she's given the medication where there are reported cases of brain death.

So, just again, to put this in context, so the idea about how this language is couched is radically going to affect. So those are the two examples that I thought of, again, not being a language expert, but we have some around the table. Maybe we

can start to give some very concrete examples to this specific language.

Thank you.

DR. BLALOCK: Dr. Wolf.

DR. WOLF: I mean, I'll just be very quick. I mean, I think this is a semantic issue that we probably will never get full agreement on as every variety of clinician may -- depending on their experience with medications, may have different interpretations, so there needs to be some accompanying clarification of the interpretation of whatever term you use and also to try to be consistent. I think that's one thing I kind of feel that's coming from it, and I completely understand how these things arise, and they should be somewhat kind of tailored to each case as you're learning it. But having that expanse to see how you use the language across multiple prescriber inserts or, you know, not just in the PLLR space, might be at least helpful to kind of start giving people a bit more a frame.

And just quickly to move to my few comments on 3B, I mean, I think -- and this is what I was trying to get at yesterday a little bit is as much as we're focused on the prescriber insert, the ability to affect physician behavior in terms of if the goal really is to at least not remove these as treatment options too soon in the context of each case -- you know, in lieu of the fact that there may be insufficient evidence, you

do need to provide some information in a way that knowing that how you inform that treatment decision making by how you release this information may affect on how confident they may feel about communicating to the patient that uncertainty so it can become a decision-making -- you know, it could be a shared decision, I think.

I think what we hear a lot from the evidence that we've been focused on, just on 3.ii and 3.iii, is when this information is insufficiently explained, especially if you do choose to prescribe a medication or you choose to de-prescribe a medication due to insufficient evidence, that may be what we would not be -- what we're trying to avoid. I think that does send a message to patients that does lead to failed treatment initiation and in cases of giving a medicine that may have risks that are not properly explained as well as obviously problems with adherence. We've seen this time and time again.

DR. BLALOCK: Thank you.

Dr. Joniak-Grant, did you have a comment? Okay.

DR. JONIAK-GRANT: Kind of opening off of what Dr. Baur said, we've got to get -- I think it's really beneficial if we have this language as plain as can be, because when someone's sitting there, they want to almost -- they're skimming through. They're trying to see -- they want to tell their patient, they're probably running behind, and if there could be some consistency in this, so something just even as simple as "data

suggests there is an association," the "data suggests it's highly likely there's an association," the "data suggests there may be an association," to just have those words where it's just like boom, boom, boom, boom, because when you start getting into all of these other things where sometimes it's, you know, "do not reliably inform," "preclude a reliable evaluation," it really starts going, well, what does that mean? And so if you could have, you know, just sort of similar phrases that you use, that would help with consistency as well.

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thanks. I just wanted to get back to the question of, well, if we have some data, how do we couch that, how do we put it out there? And I think one of the important pieces with that is to put it with what is that background risk. So you may have had, you know, six cases of whatever, neural tube defects; the baseline rate of neural tube defects in this population is X, so that it gives you an idea of is that really increased or not. And to couch it with this is, you know, very limited information but this is what we have, and to provide that background information of not only in the general population but in that specific disease population of what it is they're getting treated for.

DR. BLALOCK: Thank you.

And we've got two more comments for this question. Dr. Pleasant and Dr. Rimal. So Dr. Pleasant first.

DR. PLEASANT: Sure. This is quick. I just want to reiterate it, because I said it informally, a glossary will go a long way, whatever words you choose. And you must do it in both ways, because half the people hate going to a separate glossary and then coming back to the document, and the other half think that's absolutely the ideal way to go. So you need both, that separate glossary and rollover so that when people hit the phrase, it pops up, and then that's where you can give sort of the caveats and the added information around whatever phrase you ultimately use, because we're too large of a group to group edit.

DR. BLALOCK: Thank you.

And Dr. Rimal.

DR. RIMAL: So this is my attempt to convert 1, 2, 3, and 4 into English, and my feelings won't be hurt if you don't think this is a good conversion. I'll start with 3 and 4, "available data are not sufficient" and "available data have not reported." I thought it might be easier if more -- it might be simpler to say, "based on what we currently know," whether taking this drug leads to a bad outcome or not, so "based on what we currently know." For number 2, "limited data," I thought we might say, "we know relatively little." And then number 1, "adverse developmental outcome" -- "negative outcome for you and your baby" or "negative outcome for you or your baby."

DR. BLALOCK: Okay. I'm going to wrap this question up, then. I'm not going to -- I already sort of summarized, so let me just add, though, that we've made some great suggestions here, and you know, all of our suggestions are kind of speculation, though, and nothing replaces user testing. And I know that there was a suggestion that this was the user testing. User testing is really the intended audience, and this is not the intended audience, so I just wanted to clarify that.

So let's move on to Question 4, and I'll just tell you, my math to getting to 10 minutes to 1:00 is that let's try to discuss this and end about 12:30, because we probably do need that last 20 minutes to go around the table and all of you send your take-home messages to the FDA.

So Question 4: 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 to communicate to the public about what it does and doesn't know? And what should FDA consider in deciding whether to wait?

And there's a Part B to that as well. I think we need to do them at the same time. So suppose FDA has determined that a communication about the potential for adverse effects is needed, is necessary. What additional comments do you have about how FDA can communicate to maintain a balanced assessment

of the risk-benefit and to minimize unintended consequences?

Comments? Dr. Tracy. This is Dr. Tracy.

DR. TRACY: Dr. Tracy.

Actually, it's really kind of a question. I wrote this down yesterday as I was looking through 4, and my first thing is what we're kind of getting here is commonly referred to as a safety signal, and I just wondered, for a lot of this stuff, is there any regulatory or statutory requirements for reporting for this that we're aware of?

DR. NGUYEN: There certainly are requirements in place --

DR. BLALOCK: This is Dr. Nguyen.

DR. NGUYEN: Oh, I'm so sorry. Christine Nguyen, FDA.

There are regulatory requirements in place where, you know, if it's a serious adverse event that's not in the label, that has to be reported to us within 2 weeks. There are annual reporting requirements. So there's a host of different regulatory requirements that can provide evidence of a safety signal. Certainly, if there's a publication out there, that can provide a safety signal. So these sources can be numerous, some of which are under FDA requirements and some are not.

DR. BLALOCK: Dr. Nahum.

DR. NAHUM: Thank you. Dr. Nahum.

I think that this is a very circumspect question because I think that if you look at industry, and if you look at pharmacovigilance organizations, trying to detect and report

safety signals is what they do for a living, and these are very, very large organizations that are trying to assemble and collate and correlate information to decide when a signal is a really a signal, when it has risen above the level of noise, background noise, and it is a very, very difficult task. And I think the FDA is faced with the very same difficult task.

And I guess my one real comment here is, you know, you have to determine always what the background incidence of a particular issue is before you can decide whether a signal is, in fact, there or not, and that's when, you know, something rises above the background noise.

And so in answer to Part A, what should FDA consider in deciding when and how much to communicate to the public, if FDA were simply to be a sieve and to report every case to the public, the public would not know what to do with it. They're not very conversant in what the background risk is, what the noise is, or when a signal is a signal. So I think that the FDA cannot be a sieve and just communicate every case that comes through to them. And, in fact, there was some evidence several years ago that the FDA was not interested in putting single case reports or case series into labeling just for that reason.

So I don't think that there is a simple answer to this question. I think it's actually very complex, but I think it says that, you know, FDA is the expert that has to decide when

a signal is a signal and when to communicate it. And so asking us as a committee to weigh in as to exactly when that occurs in every circumstance is a little unfair, and I don't think we can make that determination. And I think I would say that the FDA has to process this information in each and every circumstance and decide when a signal is worth reporting so that people are aware of it and it's not just background noise.

DR. BLALOCK: Dr. Joniak-Grant.

DR. JONIAK-GRANT: I agree that the FDA needs to decide when a signal is a signal, but I think they also should be mindful of erring on the side of transparency. If we want the public to trust what's coming out and the information that they're getting, I think it's really important that the FDA not sort of stray into the realm of being paternalistic, and I know it's a very fine line, and it will vary from case to case, but I think we have to be mindful of that because once sort of the reputation goes out the door, it's hard to really have an impact with anything, especially if patients think things have been being hidden from them. And how to go about doing that, there are plenty of other people here that are well more versed in that than I am.

DR. BLALOCK: Yeah, I think that you just said, you know, err on safety. Yeah. And I'm just going to interject a comment as well because, you know, to some extent we're talking about medication risk, but there are the disease risks as well.

So when you think about erring on safety, if you had information about, say, a drug that people needed and they discontinued, then you could harm people. And so, you know, it's a little bit of a misnomer to say erring on safety by releasing more information.

DR. JONIAK-GRANT: Respond to that quickly.

DR. BLALOCK: Sure.

DR. JONIAK-GRANT: I hear what you're saying, but I also think, in some of these certain cases where they do have chronic illnesses that may be complicated, they're going to be kind of a better consumer, they're typically more aware of the information, and they're better at balancing the information. So I don't know if that would necessarily apply in all cases.

DR. BLALOCK: And I definitely agree in principle, but I just think it's easy to forget the disease risk.

Dr. Pleasant.

DR. PLEASANT: Transparency wins.

DR. BLALOCK: That was the shortest of the day. Dr. Lyerly. You get a prize.

DR. LYERLY: I'm not going to try and compete with Dr. Pleasant, but I agree that transparency is important, and I am not a fan of paternalism. But I also would say that I would agree that there are harms of indicating a signal when there isn't a real one, and once indicated, especially in the context of pregnancy, it's really hard to scale back on it.

I think about a lecture I've given about inclusion of pregnant women in research, and the person who is a full professor at UNC spoke to me about the fact that she still worries about the effect of Bendectin on her grown child and she, you know -- so anyway, these -- you know, there's an implicature to the recommendation and the language that FDA uses, which is very powerful, and I think it's important to keep that in mind.

I think some of the things that are then worth considering is if you see a signal, how likely is this -- is the worry about it to change. So if you see a signal and you think there's a very high likelihood that it's not a real signal, then I think it's worth thinking about whether it's worth communicating yet. And, also, I think what the implications of being wrong about it -- and I think this partly has to do with the disease state, but there's also public health implications. So if that changes public health programming and populations are harmed by this, then I think that these things just need to go into the calculus.

The last thing I'll say is, in my looking at these kinds of decisions, I am not clear myself about the ways in which FDA makes these decisions, which has led to confusion on my part about how to interpret those worrying communications, and while I hear that considering this on a case-by-case basis may be necessary, it seems like there may be some principles that

could be developed and made clear to the public or the prescribers so they can understand what it means when you see this kind of warning.

DR. BLALOCK: Ms. Robotti.

MS. ROBOTTI: This is a partly a question. When the FDA sees a signal that they think is significant or potentially viable or reliable, do you send an inquiry to the pharmaceutical company asking about it? Is there a moment where you take action?

DR. NGUYEN: Christine Nguyen, FDA.

So if we see a signal, do we go back to the sponsor and see if there are additional data?

MS. ROBOTTI: Certainly, at some point, if you see a signal -- I don't know if it's a lot, a few, a little, signals that there's a problem with a drug, you know, from whatever sources, that in VAERS, you see a lot of morbidity on a VAERS thing. At some point you're going to go to the pharmaceutical company and ask them about this, I assume?

DR. NGUYEN: Yes, that is correct. We actually go to multiple sources to get information. Certainly, the company tends to have a lot of information --

MS. ROBOTTI: Right.

DR. NGUYEN: -- that we would review. We also communicate with our agencies overseas, so we go to multiple places for information.

MS. ROBOTTI: Absolutely. So my suggestion would simply be that you're the best source of when to tell doctors and pregnant women, and my suggestion would be that you release and put on the PI that an inquiry has been sent to the pharmaceutical company on this particular signal. You know, it's being investigated. And that would be transparency.

DR. BLALOCK: And I'm, you know, looking at the time. I'm going to sort of start to wrap this up. I've got, I think, five folks who would like to make comments, and I think I'll draw the line there.

So Dr. Slovic.

DR. SLOVIC: This is a class of, you know, signal detection and response that goes beyond FDA. It happens in many domains like, you know, auto safety; you spot like the air bag recall, you get some incidents of anecdotal evidence, and have to -- and it starts to build, and at some point, you have to take action. It happens with regard to reports of disease. Like a few years ago it was thought that eating British beef caused this brain-wasting disease. So I would say, what should be considered? Well, the first thing is you have to take these reports seriously and quickly convene, I would say convene some task force or expertise to scrutinize the evidence and evaluate it for its reliability and import. You need to respect the fact -- this has been alluded to -- that your assertations or decisions on this are going to have tremendous not only health

impacts but economic impacts. So the British beef industry collapsed almost instantly on the report of this.

When Alar was reported to be carcinogenic to children in a TV program, overnight the -- you know, there was a huge effect on the apple industry. So we call this is a social amplification of risk. There are ripple effects, you know, that are very broad, not only affecting patient safety but the manufacturer and other sorts of things. But there are many instances of this, like emerging diseases. So maybe one can learn also by looking more broadly at how risks are managed. When things emerge and become signals, how do you respond to those signals?

DR. BLALOCK: Dr. Spong.

DR. SPONG: Thank you. I just want to make the point that not only would I recommend that that signal is taken in the context of the condition in which the signal is occurring, so you know, obviously, again, different diseases have different risks, and so taking that into context, but I also am assuming that this is specifically for the label, right? This is not for sending out an e-mail or sending out a notification or a black box warning or something that you were immediately -- this is for what's going in the label, correct?

DR. NGUYEN: This is Christine Nguyen, FDA.

This is actually more general communication. For example, we may have two publications that's -- press interest.

DR. SPONG: Right.

DR. NGUYEN: When would it be helpful or not helpful to come out with something early, because one of the feedbacks we received by being transparent -- and say there's a signal, we're looking into it, is prescribers and patients say, well, thanks, FDA, what do we do now?

DR. SPONG: Right. Okay, that helps a lot. I think the other piece that we have to take into context is what does that signal mean relative to the volume of that therapy being used? So, you know, you often will have the patient who's on something, and she'll say, you know, I've read this on the internet. And it's like, well, how many other people are taking that medication that did not have that outcome? So I think it's really important to put it into context of the volume of use of that therapy as well.

DR. BLALOCK: Dr. Goldman.

DR. GOLDMAN: Yeah, I was just going to specify that I think however you decide when to communicate it out, I would encourage some reflection and discussion within the FDA about the nimbleness with which you can manage these package inserts, because you're spending a tremendous amount of time and effort and discussion around making them a sentinel source of data and information, but then they can't be updated in any meaningful kind of real time. There are set places and moments and negotiations that occur for it to be updated. So I think, in

order to make the package insert a place of reliable information for providers, you also need to give some thought to how and when you decide to update it as the information comes in and it doesn't become a one-time thing where it's no longer the real-time place to get information.

DR. BLALOCK: Dr. Tracy.

DR. TRACY: Dr. Tracy.

I just have a couple of points. First of all, with regard to kind of the transparency issue, it's been my experience that the FDA actually has a fairly low bar of notification of things. I think that they want to be transparent, and I think they've done a good job. I think one of the mechanisms that they do this is -- and Dr. Goldman kind of touched on this briefly, is black box warnings come out. And so those safety signals are significant enough to generate enough interest that they change the PI.

In the case of one of the meds that I use, that black box was in place for 20 years. It was followed by the FDA. They asked industry to act on this and see if they could answer the concerns. It took a while. The FDA was then satisfied after those concerns were met, and they removed the block box, but in fairness, it did take almost 20 years to do that. So not particularly nimble, I would say.

The other thing which I think we also have to remember, too, is -- and we kind of touched on this a couple of times, is

the idea of class considerations. So there's two drugs that pop into my mind. One is really any corticosteroid, and the other is tacrolimus. Now, these drugs are used in multiple forms, but if you think about it, tacrolimus is used mostly for transplant rejection mostly, but it's also -- so it has a different safety profile whether it's given by IV, orally, or topically, and yet the risks that are associated with that are really very relative. And the same thing can be said for corticosteroids. An intravenous corticosteroid has a different side effect profile, pregnant or not, than say a topical one. And I just want to make sure that -- and I don't -- there's probably some statutory requirements there with regard to labeling, but we have to kind of keep that in mind, too.

DR. BLALOCK: And Dr. Nahum. And then we'll go to closing up.

DR. NAHUM: Thank you. Dr. Nahum.

I only have two brief points. One is to follow up on what was said by Dr. Nguyen, by FDA, and there was a question about signal detection, and I just want to say that as far as industry is concerned, you know, there are large pharmacovigilance departments that take this issue very, very seriously. They're all the time constantly collecting cases, spontaneously reported cases, not just the ones that go to the AERS database and FAERS database that FDA has, but also those that are reported directly to the company and through other

intermediaries.

So it is the richest database, perhaps, the spontaneous adverse event reporting, that there is, and there is something, and it was alluded to during one of the presentations yesterday, that's called a company core data sheet, and this is constantly updated with this additional information, and determinations are made not just by pharmacovigilance but also by labeling committees, or equivalence thereof, to determine when and if the FDA should be approached with, you know, a labeling change that is either a pre-approved labeling change or sometimes, you know, one that's effected immediately without even being in concurrence with FDA, depending on how serious we think it is. So we do this, and we do it all the time.

Now, the reason that -- you know, I heard the comment about everything sort of being passed on immediately to the public when it arises. The difficulty with this is when pharmacovigilance departments, such as ours, are asked to evaluate the full weight of all the evidence that's available, whether or not something is or is not a signal by FDA or by other regulators around the world, the great, great majority of the time the conclusion that's reached by everyone -- the company, the sponsor, and the regulators -- is that there should be no change to the benefit-risk ratio for the patients who have particular conditions and are being treated with the drug or biologic. So that's the reason why this information

isn't immediately passed on, because in the great majority of instances, it turns out not to be the case. So were we to pass it through immediately, we would be misinforming the public and misdirecting them potentially, both providers and people who take the medications.

The last comment that I have is just that -- and Dr. Slovic made a good point, I thought, about signal detection being something that everybody is doing all the time in various industries, just not being specific to pharmacovigilance or adverse event reporting or teratogenicity or to the FDA. This goes back really to a seminal paper in 1950 by Shannon and Weaver about how to differentiate signals from noise, and we have all been working -- there's been lots and lots and lots of work in many domains since, but it's not new, and it's not a new issue we're wrestling with here and now, but it comes up all the time.

Thank you.

DR. BLALOCK: Okay. And, again, I'll just very briefly summarize and try to do that in less than a minute. You know, a very hard question. No easy answer. And I think I definitely hear sort of the call for transparency as well as, you know, some of the issues which maybe sometimes, you know, it's not clear enough if it's a risk, so not wanting to be a sieve. So it's clearly sort of a definite, a delicate sort of a risk-benefit calculation in terms of releasing the

information. So I think I will leave it at that because I think everyone expressed things pretty clearly.

I'm looking at the watch again. I've got exactly 12:30. I'd like to start with Dr. Rimal, and we'll go around the table and, you know, looking at the clock, we've got 20 minutes to do this, tops, so if everyone can take 30 seconds to 1 minute, 1 minute tops, for a final recommendation, you know, of all the things discussed. You have a most important final recommendation for the FDA.

DR. RIMAL: I have a part A and a part B. Part A is I think we've talked about these various forms, which is to adopt a shared decision-making model, and I go back to what I was saying earlier about providing guidance to the provider to effectively communicate with their patients.

And part B is we talked a lot about benefits and risks and talking about benefits first, risks first, etc., it seems to me that there are two parts to that. One part is benefits and risks of taking the medication or continuing the medication that needs to be talked about, and then the benefits and risks of not taking the medication that also needs to be talked about.

DR. BLALOCK: And please be sure to say your name, and I'm not going to call on folks, but please be sure to start with your name.

DR. WOLF: Mike Wolf. I could say ditto, but just a more

structured approach to -- again, it may be a semantic issue. I do think you need to clarify what any new categories or new -- you need to be consistent in how you communicate the degree of evidence available so it doesn't become -- and fall back into what you had said was kind of a disaster before with A, B, C, D, X category, allow for it to be tailored and not regulate medicine. But, also, you do need to link it to helping them also communicate that uncertainty, I think, to the patient.

DR. WINTERSTEIN: Almut Winterstein. I agree that there should be some discrete categorized system. This is not the label, but that is something that would reach providers much better than anything that you would have on the label. I think that the comprehensive approach that is taken in the label makes sense, and it's consistent with the other pieces in the label that don't talk about pregnancy but everything else. So from that perspective, there are so many considerations that go into this that I would not necessarily say anything should be different for pregnancy.

With regard to talking about the risk of not taking, the information, I would again caution about the FDA's risk of not taking, the information could span an extremely broad range of indications and are extremely difficult to handle, and they would not differ from -- that is, again, something that the FDA typically does not do in the label. I mean, that's not only related to pregnancy; that would relate to anything else that

would essentially target patients. Talk to a patient about noncompliance; if you don't take this medication, then your disease will get worse, or anything like that, and I think that is just an expansion into a topic area that doesn't really belong in the label and that does belong in the hands of a provider.

With respect to the information that is in the label, I do see concerns about updating the information as new pregnancy information becomes available, and that, of course, would relate also to any kind of discrete system that is used because we do see the lack of updates quite frequently, and it's very difficult, and I completely appreciate this for the FDA to stay on top of this.

DR. SNEED: Jeannie Sneed. And I'm already starting to see consistencies in what people are saying. It's a real balancing act, and so I don't -- I'm not jealous of the fact that the physicians in this room, either the ones at FDA or the ones that are in practice, have this balancing act communicating benefits as well as risks to patients. So I would just really encourage you to talk about the benefits and then the incremental risks and make sure that that's well known. We're not always going to have perfect data, but using the best available data, developing some clear, consistent messages, plain language to communicate those outcomes.

DR. NAHUM: Dr. Nahum. Just a few major points. I'd like

to see the FDA define what a minimally clinically important difference is in terms of risk for various sorts of adverse outcomes, and this includes teratogenic outcomes of various sources or various types, I should say, and that may be variable depending on the severity of the adverse outcome itself. I'm very mindful of the fact that it's impossible to prove a negative, so nobody can ever say that something is safe in an unqualified way with a capital S, but it would go a long way, I think, for FDA to incorporate in their labeling the issues I brought up before about biologic plausibility; does something get across the placenta or does it get into breast milk, and if not, it's not that much of a worry or should not be.

And, lastly, I think that the suggestion that I floated before is really critical, to incorporate in the labeling what a baseline risk of teratogenicity is in various categories, what disease-specific risks may be in terms of the increase that they may present, medication-specific risks, and then excess risk. And that can be in the form of an attributable risk, a relative risk, a hazard ratio, an odds ratio, whatever kind of data is available.

Lastly, there should be additional structure in the PLLR system so that people know where to look and there's consistency between and amongst labels so that people are not confused when reading them.

Thank you.

MS. DUCKHORN: Hi, this is Jodi Duckhorn. Dr. Kreps had to leave, and he asked me to share with you his last two thoughts. One is establish a process for gathering additional information from expert sources about drugs that are difficult for them to classify. The expert sources can suggest best ways to classify the safety of these drugs given current evidence. And, two, establish a process for regularly seeking feedback from intended users of current drug classifications and using this information for refining the information they provide.

Thank you.

DR. SPONG: Thank you. Cathy Spong. So just very quickly, I would recommend consistency in the label, both in structure and in language, to provide context for the animal data that is included in the label, to incorporate that disease background risk, both baseline and then the disease-specific risk, and to recognize that not all risks are the same and we can't just lump those together. I'm going to give a plea not to forget lactation and that lactation is often forgotten, and to include lactation registries where you can so that we educate both the provider and the public that the safety bar has already been met for both pregnant and lactating women, and that we provide this information in a provider-friendly method using the latest technologies so that providers can get this information in a reliable and consistent way, and then testing

these messages as we can as you move forward.

Thank you.

DR. BERUBE: Dr. Berube. Three comments as well. First, test when you can, and do it concurrently. You don't have to delay everything; you can do it simultaneously. There's a lot of ways to do this. There is a huge literature out there in health risk communication and social sciences that if you tap on, I think, would be incredibly useful in coming up with unique ways of doing this type of work.

The second thing I want to mention is if you are going to try to find a way to weight the quality of the data so you give information to the prescriber, which is going to be more useful to them, please don't try to reinvent the wheel. There's a lot of these systems have already been done for a lot of different fields, everything from big data in national security all the way through other areas of toxicology.

And, finally, as a warning, I mean, I've been in nanoscience for the last 20 years and have worked with thousands of researchers. I'm one of the few social scientists in the Society of Toxicology and probably the only one who's ever published in *Nanotoxicology*, and there is an upcoming set of drugs going onto the market which cross the blood-brain barrier which offer huge treatments for a whole bunch of diseases we haven't been able to treat before, but one of the side effects is it also crosses the blood-placental barrier.

And you're going to have a whole set of challenges in the future that are going to be enormously, enormously challenging. Get ready for it, and good luck. Call on us when you need us.

DR. BAUR: Cynthia Baur. A three-part recommendation: One, use available guidelines and tools, like the plain language guidelines and the CDC index, to accurately simplify and communicate drug safety info; investigate and test new heuristics -- and I use that in the plural -- acceptable to different end users; and the third one, enlist professional societies, like ACOG and AAFP, to use their boards and members to provide regular feedback on how the label is working in the field.

DR. DIECKMANN: Nathan Dieckmann. The first thing would be to make sure to separate out the probability of a hazard or something that happened from the quality of the evidence that underlies that. You could certainly be in a situation where the probability can't be estimated and just be honest about that. That's blank. And then you have a certain amount of strength of evidence beyond that.

The other idea is for information that you expect prescribers to use at the same time, put it closer together in the message and make it clear. So if the base rates need to be used, which they should be, in the interpretation of the excess risk that may happen, make sure that that's completely clear, that information is close, and potentially provide little

nudges in there toward promoting shared decision making as much as possible, something like this information should be interpreted in light of the base rates and discussed in reference to the patient's values or something along those lines. So just make sure to include those things as much as possible and spell out that process that should be taken.

MS. ROBOTTI: Suzanne Robotti. Many excellent points already made. I'd like to push the FDA to include what information we do have, aggressively seeking out other sources versus the traditional sources. I'd encourage you to test the format of the new labeling and get feedback, not only from focus groups like this, essentially access from larger groups of doctors. I thought the concept of addressing the speed and frequency, the nimbleness of updating labels is a key thing probably outside of this, but what good is this label if it's out of date? In this day and age, we should be able to update things more quickly. I continue to be shocked that the FDA does not acknowledge that pregnancy changes all aspects of the human body and tie that to the fact that most drugs, drug approvals, have very few subpopulation divisions. So to approve a drug and assume that it's fine for pregnant women, I do not think that that should be the assumption, and it should be acknowledged that it's not. And transparency, transparency.

Thanks.

DR. LEE: This is Charles Lee. I just have a single

recommendation, and that is to include a sentence at the beginning of the narrative that is consistent across PIs in plain language that summarizes the risk so that it can be used by prescribers to relatively quickly compare the safety or uncertainty of the data of one drug to another.

DR. BLALOCK: And I don't have anything to add, so I will pass to Dr. Coombs.

DR. COOMBS: Tim Coombs. I would just like to say that I'd like to see that you keep the potential benefits of treatment prominently in the design of the message.

DR. GOLDMAN: Okay. So I've just been looking up a couple of the therapies. So, in summary, I think one thing that I've identified is to sort of streamline the process. So there are at least two drugs that were both -- the PI was updated December 2017, but one was updated within the PLLR and the other was not. And so I don't know if every time you're updating, but to streamline the process so that all of them -- if you're updating the label for any reason, you're then creating the PLLR as an integrated piece. That may bring things faster into the pipeline in that 2020 deadline.

Two is to encourage some thoughts about a point-of-care kind of distillation of information, not in substitution to the vignette or narrative prose but as an augmentation.

And then, three, to broaden the opportunities to contextualize lactation, whether that's size of the molecule,

what we know, because I think even a paucity of data is more than what we currently have for these women.

DR. PLEASANT: Andrew Pleasant. I'm always jealous now because you guys get the fun part, right?

(Laughter.)

DR. PLEASANT: No, I am not joking actually. On a larger level, just to say it once out loud, ideally we could open up an evidence-based, an evidence-gathering regulatory scheme of focus on pregnancy and lactation without creating huge amounts of social and political unrest, but that's probably not going to happen right now. Just to put the ideal out there.

So just I would encourage you to consider this discussion as a sample of data and ask yourself is it normally distributed, are we representative, your categories of analysis? Gender, clearly. Age, professional area of specialization, outlook on life, right? Apply qualitative analysis best methods to what we've said over the last 2 days; where's the overlap, where's the consensus? Remember, just because there's an outlier doesn't mean it's not important. Remember, sometimes what nobody said is a very productive area of analysis versus what was said and how it was said. And just, finally, let me know how I can help.

DR. LYERLY: Again, I think lots of great things have been said. I want to concur with others that structured and consistent language could greatly improve the labeling. I also

think communicating the view of the FDA that the drug is approved for a general adult population which includes pregnant women. I also think there are some other -- there is some other language that could be included in the preamble. An example of that would be emphasizing that risks should be considered in the context of patients' lives and health situations and that patient values are important to decision making. And, finally, that pregnancy -- remember that pregnancy introduces particular risk distortions that are not the same as other health contexts, and it is worth keeping these in mind when developing language and tools going forward.

DR. SLOVIC: Paul Slovic. I'm struck by the imbalance in the discussion over the last 2 days towards risk rather than benefit. You know, obviously, it's a balancing situation, but I think we have to be careful not to leave the benefits hidden and underappreciated while we focus on the risks. Both are obviously important.

Second is to appreciate that the human mind deals with risk primarily as a feeling, not as the result of rational calculations, and to think about how the language and other aspects of the labeling play upon our feelings, which will ultimately influence our behavior. So as we indicated earlier, words do matter, and words that might seem identical in terms of meaning may convey very different feelings. The same thing with representations of data.

Finally, just to echo what has been said about the nimbleness issue, we're in a new world of information creation and dissemination that is digital, and I think the FDA should be looking ahead towards the next generation of how we create and disseminate information.

DR. HOWLETT: Elizabeth Howlett. Again, I would second what the other members of the Committee have said and just really emphasize the need to reduce the ambiguity of the information that's now available, perhaps by some sort of categorized system, graphical displays, and so forth along that line. Of course, being as transparent as absolutely possible is important to decision makers as well.

And then I would also double the point that Dr. Slovic has just made, and that is there's multiple sources of information now that consumers are used to getting, and the same with physicians. So just assume that the message is going to be the same wherever you go and get that information. Sort of, again, make it flexible to be able to have that accessed through perhaps an FDA website, something along those lines, that can be most up to date and most useful.

DR. CAPPELLA: Joe Cappella. I'm very much concerned that in the high uncertainty cases, that with the complexity of the information that would be presented to prescribers, that the labeling process will not be used. If it's not used, then all of the concerns about linguistic choices and so on are kind of

irrelevant. So I'm very much in favor of focusing on something that has some structural shortcuts that allow the prescribers to use the information in a quick way, as quick a way as possible, but is still representative and that full information is still present.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I think it's important to rate the strength of the evidence that -- and the data that's provided. It's a good way to help providers sort of sift through information so they feel confident to assist patients in making decisions instead of feeling uncertain and pulling back from the decision-making process. When we don't know, say we don't know. When the data is poor, say the data is poor. You know, be clear and use consistently plain language that can be easily scanned, particularly in a short, sort of, doctor's appointment.

I think it would be useful to include Quick Takes for specific indications, and that's something that should be explored. It's important to include baseline risks and disease-specific risks. I know that many people that have had miscarriages, when they find out the statistics on that, they're shocked that it's so high; they have no idea that -- you know, they think it's 1 in 1,000 or 1 in 100. So I think it's really important to include that information.

Again, present information in a consistent way, using consistent phrases and a consistent organization so people can

compare and look at different medications in comparison to one another. Maybe consider including information on other places to go for information. So rather than just saying, well, here's a pregnancy registry, maybe have it be to get further information, you know, put contact stuff in there for OTIS or other groups like that so people can seek it out if they want to; providers can know where to go if they want to get some of that information.

And then, finally, I think it's just important to highlight that pain management and alleviating suffering, whether it's emotional or physical, is a really important benefit that sometimes gets overlooked.

DR. TRACY: Jim Tracy. First of all, I'm grateful for the FDA and all the work that they do, and I'm confident they'll take what we brought to them today or the last 2 days and make good use of it. That said, I would strongly encourage recognizing the complexity that whatever system of labeling we come up with is sufficiently simple to make the test useful.

The second point is really making clear, somewhere in the labeling, the risk of taking the medication but also the risk of not taking the medication.

And then, finally, with regard to user testing, in the words of -- I think it was Ronald Reagan -- trust but verify the trust which you come up with, but make sure it works.

DR. BLALOCK: Ms. Duckhorn, did you have any final closing

remarks?

MS. DUCKHORN: Thank you all for coming. We appreciated your input tremendously.

DR. NGUYEN: I get between you and your taxis, so I'll make it real short. I want to thank all of our esteemed guest speakers who have flown from all over the country to really give us valuable information. I want to thank this panel. It's been an exciting and interesting and very helpful day and a half for us here. So we really appreciate your input. I'd like to thank all my colleagues at FDA who really care about this subject, and we want to do the right thing, and I think your input has really helped us be on that path. And, lastly, I'd like to thank Dr. Blalock and Lee both for keeping us in order and facilitating such a productive meeting for us. So we have a lot of good materials to take back, and hopefully you'll see some outcomes of this discussion. Thank you.

DR. BLALOCK: Okay. And I would just like to say in closing -- and feel free to start packing up. I'd just like to say in closing that, you know, I sincerely appreciate all of the -- you know, all of the participation of the Committee members, all of the work that the FDA put in, in preparing this, as well as the guest speakers, the public, the Open Public Hearing speaker yesterday. This is an incredibly important topic and an incredibly challenging one.

So, with that, I am going to proclaim the March 6th

meeting of the Risk Communication Advisory Committee is adjourned. Thank you all again.

(Whereupon, at 12:55 p.m., the meeting was adjourned.)

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 6, 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, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY J. ATKINSON, JR.

Official Reporter