

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

+ + +

RISK COMMUNICATION ADVISORY COMMITTEE

+ + +

March 5, 2018
 8:30 a.m.

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

PANEL MEMBERS:

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

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

Free State Reporting, Inc.
 1378 Cape St. Claire Road
 Annapolis, MD 21409
 (410) 974-0947

FDA PARTICIPANTS:

JODI M. DUCKHORN
Director, Risk Communication Staff
Office of Planning
Office of the Commissioner

CHRISTINE P. NGUYEN, M.D.
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs
Center for Drug Evaluation and Research

SANDY WALSH
Press Contact

FDA SPEAKERS:

MALCOLM J. BERTONI, M.S.
Associate Commissioner for Planning
Office of Planning
Officer of the Commissioner

LYNNE P. YAO, M.D.
Director, Division of Pediatric and Maternal Health
Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

CATHERINE ROCA, M.D.
Medical Officer
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

LEYLA SAHIN, M.D., FACOG
Senior Medical Officer
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

GUEST SPEAKERS:

JENNIFER A. NAMAZY, M.D.

Representative, Vaccines and Medications in Pregnancy
Surveillance System (VAMPSS)
Physician, Allergy and Immunology
Scripps Clinic Medical Group

MICHAEL F. GREENE, M.D.

Representative, The American College of Obstetricians and
Gynecologists
Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Chief of Obstetrics, Massachusetts General Hospital

KATHERINE L. WISNER, M.S., M.D.

Norman and Helen Asher Professor
Professor of Psychiatry and Behavioral Sciences and
Obstetrics and Gynecology
Director, Asher Center for the Study and Treatment of
Depressive Disorders
Feinberg School of Medicine
Northwestern University

LAURA E. RILEY, M.D.

Representative, The American College of Obstetricians and
Gynecologists
Charles Montraville Green and Robert Montraville Green
Associate Professor
Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Vice Chair, Obstetrics
Massachusetts General Hospital

ELIZABETH CONOVER, M.S., APRN, LCGC

Genetic Counselor and Nurse Practitioner
Director, Mother to Baby Nebraska
Associate Professor, University of Nebraska Medical Center

JAMIE ZAHLAWAY BELSITO

(Patient perspective)
Founder, Effie's Grace, LLC

KAYTE SPECTOR-BAGDADY, J.D., MBioethics

Assistant Professor, Department of Obstetrics and Gynecology
Chief, Research Ethics Service, Center for Bioethics & Social
Sciences
University of Michigan Medical School

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

TRACI J. LEE, Pharm.D.
(Industry perspective)
Director, Labeling
Global Regulatory Affairs
GlaxoSmithKline

OPEN PUBLIC HEARING SPEAKER:

DANIELLE SHAPIRO, M.D., M.P.H.
Senior Fellow
National Center for Health Research

INDEX

	PAGE
CALL TO ORDER - Susan J. Blalock, Ph.D., M.P.H.	7
PANEL INTRODUCTIONS	7
CONFLICT OF INTEREST STATEMENT - Lee Zwanziger, Ph.D.	12
OPENING REMARKS - Malcolm J. Bertoni, M.S.	15
FDA PRESENTATIONS	
Communicating Information about Risks of Prescription Products and Vaccines Used During Pregnancy - Lynne P. Yao, M.D.	19
An Evolution of Labeling Information for Pregnant Women: PLLR History and Background - Catherine Roca, M.D.	26
Fulfilling the Intent of PLLR: Current Approaches and Challenges - Leyla Sahin, M.D.	46
GUEST SPEAKER PRESENTATIONS	
Physicians' Perspective of the New Pregnancy and Lactation Labeling: Survey Results - Jennifer A. Namazy, M.D.	61
Communicating Risk in an Environment of Uncertainty - Michael F. Greene, M.D.	70
Prescribing for Pregnant Psychiatric Patients: Progress Report - Katherine L. Wisner, M.S., M.D.	82
Communication: Advisory Committee Update on Immunization Practices (ACIP) Update - Recommendations and Vaccine Uptake by Pregnant Women - Laura E. Riley, M.D.	99
Communicating Teratogen Information Effectively: The Teratogen Information Service (TIS) Perspective - Elizabeth Conover, M.S., APRN, LCGC	113
OPEN PUBLIC HEARING	
Danielle Shapiro, M.D., M.P.H.	142

INDEX

	PAGE
GUEST SPEAKER PRESENTATIONS	
Patient Perspective: Pregnancy and Lactation Labeling Rule - A Modern Day Medical X Factor - Jamie Zahlaway Belsito	146
Pregnancy and Lactation Labeling: A Law and Ethics Perspective - Kayte Spector-Bagdady, J.D., MBioethics	165
Pregnancy & Lactation Labeling Rule (PLLR): Industry Perspective - Traci J. Lee, Pharm.D.	187
CLARIFYING QUESTIONS	209
CHARGE TO COMMITTEE/COMMITTEE DISCUSSION	247
Question 1	270
ADJOURNMENT	289

M E E T I N G

(8:00 a.m.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 is focused on medication safety and adherence.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 Thank you.

17 DR. BLALOCK: Thank you.

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

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

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

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

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

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

- 16 - Reduce the burdens of addiction crises that are
17 threatening American families;
- 18 - Leverage innovation and competition to improve
19 healthcare, broaden access, and advance public health goals;
- 20 - Empower consumers to make better and more informed
21 decisions about their diets and health, and expand the
22 opportunities to use nutrition to reduce morbidity and
23 mortality from disease; and
- 24 - Strengthen FDA's scientific workforce and its tools for
25 efficient risk management.

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

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

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

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

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

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

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

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

25 Of course, there are many other contributions. The

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

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

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

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

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

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

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

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

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

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

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

1 our communications on prescription drug and biological
2 products.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 So what about pregnancy-specific information? As I think
13 probably all of you in the room know, that on December 4th,
14 2014, FDA published a final rule relating to information in
15 prescription product labeling for pregnancy and lactation. And
16 the goal of this rule was to improve the communication of
17 information related to pregnancy and lactation, also to improve
18 on the information we provide related to when pregnancy
19 testing/contraception should be used, and of course, any
20 effects on male or female fertility.

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

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

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

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

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

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

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

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

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

13 Thank you.

14 DR. BLALOCK: Thank you, Dr. Yao.

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

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

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

1 So just to provide some background, in the United States,
2 there are approximately six million pregnancies every year, and
3 about half of pregnant women report taking at least one
4 medication in pregnancy. And in a study that was done a couple
5 of years ago where they looked at data from interviews of over
6 30,000 women who provided information about their antenatal
7 medication use, researchers found that on average, women take
8 between three and five medications at any point during
9 pregnancy.

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

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

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

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

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

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

13 And as a result of these amendments, the animal
14 developmental toxicity data increased, and also reports about
15 medication use in pregnancy increased as well. And so by the
16 1970s, clinicians were really faced with a large body of
17 information, but it was rather unwieldy and difficult to
18 interpret.

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

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

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

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

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

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

1 teratogenic risk.

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

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

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

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

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

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

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

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

1 because PLLR had not been published in its final form.

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

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

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

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

25 Animal data have to be put in the context of human

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

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

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

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

22 8.2, Lactation, again has a mandatory risk summary
23 subheading. Clinical considerations, for example, if there's a
24 recommendation to pump and discard milk for after a certain
25 number of hours after exposure to medication, that would come

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

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

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

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

21 Thank you for your attention.

22 DR. BLALOCK: Thank you, Dr. Roca.

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

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

5 Dr. Slovic.

6 DR. SLOVIC: Thank you.

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

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

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

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

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

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

10 DR. BLALOCK: Dr. Spong.

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

13 My question relates to Slide 19, where you have outlined
14 very clearly the overview of the changes to labeling and the
15 use of specific populations. And I just wondered why, under
16 8.2, there wasn't a similar place for lactation registries.

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

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

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

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

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

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

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

20 DR. BLALOCK: Dr. Nahum.

21 DR. NAHUM: Yes, thank you.

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

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

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

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

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

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

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

14 DR. BLALOCK: Dr. Goldman.

15 DR. GOLDMAN: Hi. Yes. Thank you.

16 I just -- general comment: One, as someone, as a
17 practicing neurologist, not sort of at the edge of this, I
18 think this is incredibly important work and that tremendous
19 strides have already been made in the efforts that have been
20 put forward. My question relates more to understanding the
21 scope of what needs to be done. Specifically, will all
22 FDA-approved drugs -- so this timeline that you have in
23 Slide 7, does that include or is that inclusive of all
24 approved -- oh. Slide -- or maybe it was the earlier, the
25 2018, 450 projects, 2019. Maybe it was Slide 7 from an earlier

1 deck.

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

8 DR. ROCA: It's on page 2.

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

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

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

16 DR. ROCA: Sure.

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

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

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

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

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

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

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

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

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

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

14 So Dr. Lyerly and then Dr. Slovic.

15 DR. LYERLY: Thank you.

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

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

1 safety profiles that pregnancy introduces.

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

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

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

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

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

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

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

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

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

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

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

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

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

16 DR. BLALOCK: Thank you.

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

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

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

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

10 DR. BLALOCK: Thank you.

11 So thank you, Dr. Roca.

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

14 DR. SAHIN: Good morning, everybody.

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

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

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

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

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

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

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

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

1 these studies may not be representative of the general
2 population.

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

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

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

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

1 Disadvantages include the recall bias, because sometimes
2 women may be interviewed about their drug exposure up to
3 2 years after they've had their delivery. And because there
4 are multiple statistical comparisons that are conducted, we
5 tend to see chance findings.

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

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

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

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

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

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

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

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

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

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

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

1 Now we focus our efforts on developing the messaging.

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

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

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

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

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

25 This next slide has the animal data presented in more

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

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

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

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

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

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

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

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

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

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

25 The case control study found an association with isolated

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

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

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

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

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

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

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

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

1 that occur.

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

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

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

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

1 difficult to communicate in labeling.

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

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

10 DR. BLALOCK: Thank you, Dr. Sahin.

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

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

20 DR. SAHIN: Thank you for your question.

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

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

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

8 I saw Dr. Cappella.

9 DR. CAPPELLA: Just a question of information.

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

16 DR. SAHIN: Thank you for your question.

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

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

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

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

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

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

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

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

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

4 DR. BLALOCK: Thank you, Dr. Sahin.

5 DR. SAHIN: Thank you. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 observe 57 physicians across specialties.

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

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

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

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

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

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

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

15 I'll take questions.

16 DR. BLALOCK: Thank you, Namazy.

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

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

21 MS. ROBOTTI: I'm Suzanne Robotti.

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

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

1 today.

2 DR. BLALOCK: Dr. Goldman.

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

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

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

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

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

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

1 material that's being discussed here.

2 (Off microphone comments.)

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

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

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

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

12 So Dr. Greene.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 And several years later, 4 years later, published again
20 from the same database, this time by Sonia Hernandez Diaz at
21 the Harvard School of Public Health, using Lew's database, wrote
22 that "We published a risk of oral clefts of 7.3 per 1,000 among
23 684 users of lamotrigine monotherapy. With a larger sample of
24 1,500, the estimate's now 4.5 per 1,000." The lower confidence
25 bound was still 2.2, but other studies have -- and she

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

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

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

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

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

1 treating epilepsy during pregnancy.

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

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

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

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

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

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

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

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

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

25 The impact of medicolegal environment is undeniable. This

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

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

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

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

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

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

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

17 DR. BLALOCK: Thank you, Dr. Greene.

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

20 Dr. Nahum.

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

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

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

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

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

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

2 So it is relative and relevant. But safety is relative.

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

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

13 DR. BLALOCK: Thank you, Dr. Greene.

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

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

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

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

1 what psychiatrists want to see in labeling.

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

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

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

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

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

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

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

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

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

25 The other area that we're concerned about with depression

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 treated illnesses are also important for a healthy pregnancy.

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

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

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

25 The study that Allen Mitchell did about the number of

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

10 The graph is a little misleading in that 8% of women were
11 exposed to antidepressants. In this same study, about 2% to
12 2½% of women continued those antidepressants in pregnancy. And
13 those were likely to be those women who made that choice
14 because they felt as though their risks of not continuing were
15 very high.

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

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

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

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

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

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

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

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

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

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

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

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

1 understand that first.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. BLALOCK: Thank you, Dr. Wisner.

11 Any brief clarifying questions for Dr. Wisner?

12 Dr. Goldman.

13 DR. GOLDMAN: Hi. This is Myla Goldman.

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

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

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

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

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

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

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

25 DR. BLALOCK: Thank you very much.

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

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

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

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

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

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

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

1 1918, 1957, and the obviously, the most recent in 2009,
2 pregnant women did not fare well in the flu season.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 And it is very clear, and has been shown in multiple
5 studies in addition to the internet surveys, that if physicians
6 or midwives or whoever the OB provider is suggest to a patient
7 that they get the flu vaccine, they're much more likely to get
8 it. And so at that point, you know, more women get it if
9 they're suggested to, but still the coverage rates are around
10 50%.

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

15 And so this is something that has come up, which is really
16 kind of concerning. And this is again using the internet
17 survey. But this is looking at earlier in 2017, just a quick
18 snapshot, where it looked like way fewer women were getting
19 vaccinated this year than would have been anticipated, only
20 35%.

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

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

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

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

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

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

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

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

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

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

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

1 what happens.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 It looks like Dr. Berube has a clarifying question.

2 DR. RILEY: Yes.

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

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

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

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

19 DR. RILEY: MMR.

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

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

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

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

13 DR. BLALOCK: And that was Dr. Robotti.

14 Dr. Slovic.

15 DR. SLOVIC: Thank you. Paul Slovic.

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

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

1 is that going to communicate on the affective side?

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

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

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

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

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

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

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

1 My single disclaimer, that I receive information, as do another
2 11 teratogen information services, that comes through HRSA for
3 support of educational research and service activities.

4 And so we've mentioned OTIS and MotherToBaby a couple of
5 times today. Just to let you know a little bit about us, we
6 are a completely nonprofit, as we say, nonprofit group of about
7 100 people who do clinical teratology. So we're interested in
8 the applied part of all of this. And we get together to talk
9 about our problems with lack of data, what do we do with
10 conflicting data, how do we convey this information in a way
11 that people can make decisions, in terms of doing it.

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

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

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

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

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

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

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

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

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

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

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

13 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 I had this whole little vocabulary of it, and I thought I
21 was really just doing a fabulous job with that. And then I
22 read some of the data on the fact that, for example, there was
23 a study that the word "likely" included anything from 0.5 to
24 0.99 chance of happening. Oh dear.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 providers, say oh my gosh.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 DR. BLALOCK: That's what I thought.

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

11 DR. NAHUM: Yes. Dr. Nahum.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. BLALOCK: Thank you.

21 MS. CONOVER: Thank you.

22 DR. BLALOCK: Dr. Joniak-Grant.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 a lot of people is hard.

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

4 MS. CONOVER: Yes. I bet you will.

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

7 DR. LYERLY: So thank you for the talk.

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

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

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

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

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

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

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

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

1 about my 3% background risk?

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

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

14 DR. BLALOCK: Thank you very much.

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

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

24 Oh, some other very important things. There's a room in
25 1504, that's left out of the room, for members to eat. And

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

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

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

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

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

(12:49 p.m.)

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

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

DR. ZWANZIGER: Thank you, Dr. Blalock.

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

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

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

1 of the meeting. Dr. Shapiro.

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

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

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

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

25 Number two, how effective are the communications provided

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

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

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

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

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

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

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

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

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

1 perceptions.

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

6 Thank you for the opportunity to share our perspective
7 today.

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

10 Dr. Robotti.

11 DR. SHAPIRO: Yes.

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

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

24 DR. BLALOCK: Thank you.

25 Does anyone else in the audience wish to address the

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

3 (No response.)

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

8 (No response.)

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

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

14 MS. ZAHLAWAY BELSITO: Thank you very much.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 counteract negative side effects."

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

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

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

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

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

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

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

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

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

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

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

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

1 completely jumped over my skis here in the beginning.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 DR. BLALOCK: Thank you very much.

19 Do any of the Committee members have brief clarifying
20 questions?

21 Dr. Joniak-Grant.

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

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

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

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

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

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

4 DR. BLALOCK: Dr. Tracy.

5 DR. TRACY: Thank you.

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

13 MS. ZAHLAWAY BELSITO: Thank you for the question.

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

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

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

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

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

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

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

25 Where I think, when it comes to pain management or

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

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

13 DR. BLALOCK: Dr. Goldman.

14 DR. GOLDMAN: Myla Goldman.

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

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

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

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

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

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

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

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

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

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

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

18 DR. BLALOCK: Dr. Lyerly.

19 DR. LYERLY: Thank you for that presentation.

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. BLALOCK: Thank you very much.

11 MS. ZAHLAWAY BELSITO: Thank you.

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

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

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

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

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

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

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

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

25 But she needs adequate information to do so, presented to

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

7 And then regulators -- government workers are people too.
8 I'm a former fed. Regulators have their own interests, right.
9 And as Dr. Yao went over for us, FDA, we believe in the
10 mission. They're here to ensure the safety, efficacy, and
11 security of human drugs.

12 And we've already talked a little bit about the importance
13 of the rallying cry of the thalidomide disaster to this. But
14 this has really led to very profound safety and efficacy
15 evaluations, once again, to help and protect the patient.

16 And the drug developers and manufacturers and marketers
17 also bring to the table their own interests. Most of them are
18 for-profit entities, but they're there to develop and market
19 safe and effective products that clinicians will prescribe.

20 And then, of course, all of these parties have interests
21 between them, the regulators and the regulated market. Drug
22 developers and manufacturers have direct relationships with
23 clinicians either through advertising, detailing, marketing,
24 and then regulators and clinicians also have their own
25 relationships. So this can get very complex.

1 And then, of course, we have our legal constructs. And
2 I'll go into this a little bit more deeply because that's what
3 you flew a lawyer here to do. But essentially, some of the
4 main ones are, of course, medical malpractice claims between
5 the patient and her clinician, which hopefully are rectified or
6 absolved through the informed consent process.

7 There are sometimes direct product liability claims from
8 the patient against drug manufacturers and developers, which
9 they hope will be somewhat rectified by the learned
10 intermediary doctrine, which I'll talk a little bit more about.
11 And then, of course, we have labeling regulations, whereas
12 feds, the FDA regulates the industry to ultimately assist the
13 doctor in doing that informed consent practice.

14 So to talk a little bit more about products liability, so
15 drug and device cases are a huge portion of our federal case
16 load. And as Professor Conover also talked about, we know that
17 15% to 20% of pregnancies already end in miscarriage, and up to
18 3% of pregnancies are affected by birth defects.

19 And so in order to have a tort law claim, you have to have
20 a duty, breach, causation, and an injury. We know that doctors
21 have a duty of care towards their patients, and this is a
22 really large potential injury base that we don't necessarily
23 know what caused those injuries. We don't necessarily know
24 what happened, why the person miscarried, why there's a birth
25 defect. But that is a large pool of potential litigants. And

1 as Professor Conover said, all risk must be causal is something
2 that many patients subscribe to.

3 And then we have the learned intermediary doctrine. So
4 whereas in general products liability, manufacturers have a
5 duty to warn the end user of a product, for prescription drugs,
6 the clinician herself acts as a learned intermediary between
7 the manufacturer and the patient, such that generally a
8 manufacturer's duty to warn is fulfilled by warning the
9 clinician, who then has a tailored conversation with the
10 patient.

11 So as a quick example, I think it was just mentioned and
12 not gone that much into, is a case study of Bendectin, which
13 was authorized by the FDA in the 1950s for nausea and vomiting
14 caused by pregnancy and was used across the world for almost 30
15 years and in over 33 million pregnant women.

16 But the first case alleging a birth defect from Bendectin
17 was filed in the U.S. in 1977, and the FDA convened a panel to
18 review the scientific literature and actually found no
19 association between the drug and birth defects. But in 1983,
20 Merrell Dow decided to pull the drug off the U.S. market
21 because there wasn't enough of a profit margin between selling
22 the drug and their litigation and insurance costs.

23 And some subsequent research even found that when
24 Bendectin was pulled from the market, hospitalizations for
25 these pregnant women for nausea and vomiting increased rapidly.

1 So, then again, that's an example of sort of a failure of a
2 cost-benefit analysis.

3 And then we have medical malpractice claims. And whereas
4 general clinicians believe their risk of being sued is much
5 higher than it already is, OB/GYNs are right; they get sued a
6 lot. And a recent ACOG survey found that 74% of OB/GYNs have a
7 professional liability claim filed against them during their
8 career, and that's an average of almost three claims per
9 clinician in their lifetime. And almost half of these
10 clinicians reported making a change to their practice in
11 response to these specific liability concerns.

12 And we also know that doctors are supposed to act within
13 the standard of care, again, duty, breach, causation, injury.
14 And so we talked about the duty, we talked about the injury.
15 But a breach of that duty is usually going to be measured
16 against the standard of care.

17 So the law doesn't generally prospectively prescribe a
18 specific standard of care. And it's actually based on evidence
19 of customary practice or what a reasonable practitioner would
20 do in a similar situation. But it's important to note that
21 that standard of care is not necessarily synonymous with best
22 or evidence-based medicine.

23 So it's not evidence of effectiveness, but evidence of
24 practice. And clinicians in the past have been found liable
25 for violating a standard of care that's not actually supported

1 by the best or most recent data.

2 And so I actually had a recent article that came out with
3 my colleagues at the University of Michigan -- Ray De Vries,
4 Lisa Harris, and Lisa Kane Low -- that there are situations in
5 which practitioners actually who are concerned about liability
6 implications stay away from -- they're sort of risk averse to
7 the standard of care. But if all clinicians are acting in ways
8 that are risk averse to the standard of care, that can actually
9 serve to shift the standard of care.

10 So then they're getting -- you know, judged against these
11 risk-averse actions as opposed to what it should be, which we
12 described as the standard of care sprawl. And we used the
13 example of electronic fetal monitoring when we were doing that
14 because there is many, if not most, circumstances in which
15 electronic fetal monitoring is actually not prescribed. But
16 you can see where this might also be very applicable to
17 implications for prescribing drugs for pregnant and lactating
18 patients.

19 And then we have informed consent. And sort of the
20 classic iteration of what informed consent means is it requires
21 capacity, information, and freedom from coercion, but we're
22 here to focus on the information component. And, you know,
23 it's important to note that just because we get informed
24 consent doesn't necessarily mean the clinician doesn't have to
25 meet the standard of care. They do. And just because you're

1 acting within the standard of care doesn't mean you don't have
2 to get informed consent. You need both.

3 And what we're trying to balance in this informed consent
4 discussion is both the autonomy of the patient -- so patients
5 must not only give consent, they must give consent that is
6 informed -- but also it must be tempered by the clinician's
7 ethical duty of beneficence.

8 So, for example, clinicians are supposed to take into
9 consideration the patient's mental and emotional condition,
10 their level of education, their own values and priorities. And
11 this is something that only the clinician can balance herself
12 with the patient sitting in front of her, because clinicians
13 and patients obviously come to the table with completely
14 unequal information. And that's why the patient's there in the
15 first place.

16 And there is this real tension between autonomy and
17 beneficence that needs to be tailored. We need to give the
18 patient enough information to enable a knowledge decision, but
19 not so much that the patient is confused or overwhelmed. And
20 this fine art of disclosure balance plays a large role in this
21 last area, which is the labeling regulations.

22 So as the Supreme Court has summarized this in the past,
23 ultimately the manufacturer bears responsibility for the
24 content of its label at all times. Quote, "It is charged both
25 with crafting an adequate label and with ensuring that its

1 warnings remain adequate as long as the drug is on the market."

2 And this intersects with the standard of care in sometimes
3 interesting and sometimes confounding ways. So the majority of
4 jurisdictions in the U.S. accept drug labeling as evidence in
5 support of the standard of care, in addition to expert
6 testimony. So it's not the sole determinant of what the
7 standard of care is, but it can provide significant assistance
8 in establishing it. And only a few jurisdictions actually have
9 held that labeling is, on its face, the standard of care.

10 The American Medical Association recently came out with
11 its own position statement, which reads, quote, "Official
12 labeling should not be regarded as a sole standard of
13 acceptable or accepted medical practice, nor as a substitute
14 for clinical judgment or experience, nor as a limitation on the
15 usage of the drug in medical practice."

16 But just like informed consent between the clinician and
17 the patient, again, these drug labels are about disclosure
18 balance. And in 2006 FDA wrote, somewhat optimistically it
19 turns out, that labeling should establish both a floor and a
20 ceiling of disclosure.

21 Quote, "Given the comprehensiveness of FDA regulation,
22 additional requirements for the disclosure risk are not
23 necessarily more protective of patients. Instead, they can
24 erode and disrupt the careful and truthful representation of
25 benefits and risks that prescribers need to make appropriate

1 judgments about drug use. Exaggeration of risk could
2 discourage appropriate use of a beneficial drug."

3 And then in 2009, that other branch of government, the
4 court system, said check on the executive one. And in this
5 famous case, a Vermont musician went to a clinic for a
6 treatment of migraine and received an IV push of the anti-
7 nauseal Phenergan rather than an IV drip. Phenergan entered
8 the musician's artery. She developed gangrene, and
9 unfortunately, her entire forearm had to be amputated.

10 So Wyeth labeling had warned against intra-arterial
11 injection and said it was preferable to administer its drug via
12 IV drip, but it did not specifically warn against IV push. And
13 Wyeth argued that the fact that FDA had approved its labeling,
14 so that if this federal agency had approved its labeling, would
15 preempt any state tort law claims.

16 And, generally, manufacturers may only change a drug label
17 after FDA approval, but there is a change in being effective
18 regulation that allows drug manufacturers to do so in a case of
19 additional risk or contraindications.

20 And, therefore, the court found that because there is this
21 exception, there was an avenue for manufacturers to update the
22 label even before FDA had approved it, and therefore, it was
23 not impossible to comply with both federal and state and that
24 the FDA labeling regulations did not preempt it, which means
25 that even though FDA might say that is the appropriate label,

1 there might be state tort law claims that might still be levied
2 against clinicians for prescribing according to that label.

3 So as you can see, there are lots of different stakeholder
4 interests that might or might not fully align with all of the
5 legal mechanisms that we've set up to protect them. But so,
6 ultimately, I'm going to clear away some of this noise and
7 focus on what we're really here about, and what we're really
8 here about is this informed consent discussion.

9 And in order to have a really clear conversation about
10 informed consent, I think we need to introduce another
11 stakeholder, which is data tracking and research. And it's
12 that data tracking and research that's ultimately going to
13 generate the kinds of peer-reviewed publications that we need
14 to inform both clinicians directly, as well as the drug
15 manufacturers, such that FDA can require, then, that they
16 disclose back to the clinician such that she can have the best
17 informed consent discussion possible to the pregnant and
18 lactating woman.

19 And, of course, these are regulated by yet another
20 regulatory regime, and I hate to even say it out loud before
21 July, but those are the human subjects research regulations.

22 So I'm a research ethicist at heart, and so I must have a
23 slide on the research ethics of this. And certainly want to
24 acknowledge all of the important groundbreaking work that has
25 come before me on this, particularly Drs. Annie Lyerly, Maggie

1 Little, and Ruth Faden, and their Second Wave Initiative; the
2 Office of Research in Women's Health; the Task Force on
3 Research Specific to Pregnant Women and Lactating Women; and
4 some of the IOM Committees, who have found time and time again
5 a sort of unnecessary exclusion of pregnant women from research
6 and many IRBs considering pregnancy, on its face, a cause for
7 exclusion.

8 And we really need to continue to include pregnant and
9 lactating women in this research, not only to help future women
10 and their babies like them but also because, quite frankly,
11 some of this research has potential benefits to these women,
12 and they're being excluded from being involved in them, because
13 quite frankly, if we're not conducting research with pregnant
14 and lactating women, we're just experimenting on them all.

15 And the typical approach of postmarket drug surveillance
16 is quite biased. We know. We've talked about this. Dr. Sahin
17 went into this for us. But, you know, if we only report
18 adverse events when clinicians or patients bother to do so,
19 they're much more likely to be major, and they don't give us
20 the necessary prevalence data against which to weigh them.

21 And so what we really need to be doing is gathering this
22 data over all facets, again, guidance and encouragement of
23 pregnancy exposure registries, many of which are run by the
24 manufacturers themselves, clinical data registries by
25 professional organizations such as ACOG, retrospective cohort

1 studies.

2 But all of these are still ultimately just data silos,
3 right. You have to go to all of these different registries;
4 you have to pull all this different information. We've heard
5 about busy clinicians not necessarily having time to amalgamate
6 all of this information themselves. So we really need to
7 continue to encourage broad data generation sharing and use.

8 So, moving forward, this is my last slide. What does this
9 mean for us? So we are here today to talk about disclosure
10 standards. And hopefully I've given some helpful information
11 about relevant legal constructs and liability towards that.
12 And, certainly, we have the right people around the room, the
13 preeminent experts on communication of risks and health
14 benefits here already.

15 But ultimately here, the outcome of interest to us is the
16 improved health of the pregnant and lactating women and their
17 babies. And this theme that we've heard throughout the day is
18 that this is actually ultimately an information problem to
19 which the disclosure issue is actually secondary.

20 So I was the Associate Director for President Obama's
21 Bioethics Commission for 6 years, which is also a federal
22 advisory committee. But I'm not a fed anymore. I'm an
23 academic, so I get to say stuff like this. But just like we
24 have data silos in clinical care, in research we have health
25 policy silos in the federal government, right.

1 And so we have an NIH, an FDA, and OHRP, and the Office of
2 the Secretary, and they really are all working towards the same
3 overarching goals -- I believe that, they believe that -- but
4 not necessarily in the most consistent ways possible.

5 And so, yes, methods and order and type of disclosure is
6 critical. And we should focus on that, and we should work
7 towards the things that we have power to achieve. I
8 acknowledge that. But just as critical is having the best
9 information to disclose.

10 And so I would encourage you, in your deliberations, to
11 also not lose the forest for the trees and ensure that labeling
12 regulations and your communication recommendations enable and
13 align with best practice methods, such as observational data
14 gathering and research incentives, to make sure we're
15 disclosing the most helpful information possible in the best
16 ways possible.

17 Thank you.

18 DR. BLALOCK: Thank you very much.

19 Dr. Nahum, you have a brief clarifying question?

20 DR. NAHUM: Yes, I do.

21 You know, just looking at Slide 5, I have a question,
22 because I think you said something perhaps that you didn't mean
23 to say. And I'm reading the top bullet point, which says drug
24 and device cases, these comprise almost 45% of the federal case
25 load.

1 I want to refer back to the FD&C Act, as amended, and the
2 preemption clause that exists there for medical devices. This
3 is broad. It's in force. And it has pretty much limited
4 medical malpractice liability vis-à-vis product liability for
5 manufacturers as that CDRH approval of medical devices with
6 appropriate labeling, with appropriate manufacturer packaging,
7 labeling, distribution effectively exempts all manufacturers
8 from tort liability for those products.

9 Now, if you meant to say combination products, then I
10 understand this, in the case of the drug device combination or
11 biologic device combination or another combination which does
12 involve a medical device. But in and of itself, I do not
13 believe that medical devices would comprise any substantial
14 portion of this 45%.

15 MS. SPECTOR-BAGDADY: Yeah. I think that that's really
16 fair. It's a good clarification that certainly prescription
17 drugs and medical devices are regulated differently because of
18 this explicit as opposed to implicit preemption in the medical
19 device amendments. I don't have specific data. The
20 researchers who put out the 45% didn't break down the drugs
21 versus devices versus OTC, but I'm happy to look more into that
22 and send you it. But I don't have that on hand.

23 DR. BLALOCK: Any other brief clarifying questions?

24 Dr. Baur.

25 DR. BAUR: Cynthia Baur.

1 So my question has to do with your model for stakeholders.
2 And I'm curious why you left out politicians, since they
3 provide the policy framework. And I'm thinking, if in our
4 deliberations we come to the conclusion that maybe it's a
5 combination of information and policy, I'm just wondering how
6 your framework would accommodate that.

7 MS. SPECTOR-BAGDADY: Yeah. I like that observation. I
8 guess when I was thinking of stakeholders, I didn't think of --
9 perhaps erroneously -- politicians as bringing their own
10 personal interests to this table that was somehow different
11 than that of the best interests of patients and clinicians and
12 the U.S. health system.

13 But, certainly, Congress has a lot of power to act in this
14 space, particularly as we were just discussing in the area of
15 express preemption. So I don't think that that would be wrong
16 to add them as a stakeholder, but that was my thinking as sort
17 of when we're really boiling down to the lobbying and the
18 interests and the advocacy, who we're working towards, it's
19 really these entities.

20 DR. BAUR: Well, I think, particularly in light of our
21 previous speakers' observations about really the politics
22 around motherhood, that I would definitely encourage you to
23 think about politicians having their own spot in your map
24 because I don't think that -- as a mother, I don't know that
25 politicians' interests always align with mine.

1 MS. SPECTOR-BAGDADY: I would agree with you. I think
2 that's a fair addendum.

3 DR. BLALOCK: Dr. Nahum.

4 DR. NAHUM: Thank you. I do have one more clarifying
5 point here.

6 Towards the end of your talk, I think you were alluding to
7 the fact that real-world data of various sorts, especially with
8 approved drugs and biologics, would be useful to collate,
9 process, and ultimately analyze to be able to come up with
10 better paradigms with regard to benefit-risk ratios in various
11 settings for different types of drugs and biologic products.

12 I guess I have a comment and a question about that. When
13 we collect real-world data, even when these drugs are approved,
14 as far as confounders are concerned, there are those that are
15 known, there are those that are unknown, and then there are
16 unknown unknowns. It may be potentially possible in large
17 databases that are consolidated to control for some of these in
18 some cases.

19 But in the case of biases, and I mean here, prescriber
20 biases, access biases, patient selection biases, etc., these
21 cannot be controlled. They cannot be expunged, and they cannot
22 be eliminated. And this will result in all cases in biased
23 findings, biased results, and will cause people, patients,
24 practitioners, institutions, and governments to believe, in
25 many cases, what is simply not true.

1 So how do you reconcile this with the last several slides
2 that you presented, advocating for the use of this type of
3 poorly or uncontrolled data to better inform us as to what to
4 do?

5 MS. SPECTOR-BAGDADY: Well, so one possible solution to
6 poorly and uncontrolled data is power. And that's why we so
7 often don't find out about adverse side effects to drugs and
8 devices until they go onto the market. And instead of having
9 hundreds of people enrolled in our clinical trial, suddenly we
10 have hundreds or tens of thousands of people who are actually
11 taking the drug.

12 And I acknowledge that certainly there does not exist an
13 ideal solution for this at the time, which is why I closed with
14 the argument that whereas we don't have the ideal solution yet,
15 what I would encourage us to do as we work towards it is at
16 least not work in ways that undermine the ideal solution, and
17 that we need to keep into consideration, as we make all of
18 these smaller decisions, how exactly to order this, how to
19 disclose this, what should we do in X, Y, Z cases, that the
20 ultimate goal is this kind of data generation and data building
21 that will help us all.

22 And I think that the more data sharing and the more data
23 use we can do, the better that will become. But I agree that
24 we are very far from the ideal solution at this point.

25 DR. BLALOCK: And one final clarifying question,

1 Dr. Cappella.

2 DR. CAPPELLA: Joe Cappella. I just wanted to check on
3 something that I think I heard you say, or that I may have
4 misinterpreted, and that was the comparison between standard of
5 care and labeling information, and that in some senses, that
6 just because there was an accepted labeling information for a
7 pertinent drug, that may or may not be the standard of care.
8 So the standard of care may be to ignore the labeling or to put
9 it in a subsidiary position. Is that correct, as far as
10 you're -- as I understood you to be saying?

11 MS. SPECTOR-BAGDADY: So different jurisdictions have gone
12 different ways, because ultimately this is a state law
13 question. But the majority of jurisdictions have found that
14 labeling, in addition to expert opinion saying that yes, this
15 labeling is in fact what most practitioners follow in this
16 situation, is generally accepted as a standard of care.

17 And there are only a few jurisdictions which don't require
18 that additional expert testimony that testifies that yes, the
19 labeling is in fact the standard of care, and they just accept
20 the label on its face. So it's a bit diverse across the
21 states.

22 DR. CAPPELLA: So what that might mean is that that in
23 some jurisdictions, that the labeling might not be a motivation
24 to the prescriber because it isn't necessarily the standard of
25 care.

1 MS. SPECTOR-BAGDADY: Yes, that's correct. And, in fact,
2 that's one of the concerns that I was trying to talk about,
3 whereas if people are acting sort of in overly risk-averse
4 ways, even though the labeling might say it's okay to do this
5 in this situation, if everyone in a practice area in a
6 geographic region is actually working in more risk-averse ways,
7 above and beyond that which the label states, that could be the
8 standard of care that the court finds.

9 DR. BLALOCK: Yeah. Dr. Nguyen, did you have a comment
10 that you wanted to make?

11 DR. NGUYEN: Thank you. I actually have a question.

12 Thank you for that excellent presentation. You had
13 mentioned that, I think it was 60, 70% of OB/GYNs have been --

14 MS. SPECTOR-BAGDADY: Yeah, 74%.

15 DR. NGUYEN: -- served a notice of lawsuit. And about
16 half of them changed their practice afterwards. Could you
17 clarify on what those changes were?

18 MS. SPECTOR-BAGDADY: Yeah. So that was sort of an
19 amalgamated percentage that included a lot of different things.
20 The ones off hand that I can tell you about are, for example,
21 ordering tests that the clinician didn't necessarily feel were
22 medically necessary but the patient requested them. And the
23 clinician felt under some duty to order that just because they
24 were worried that the patient was going to get upset or that
25 something might happen and they might be sued.

1 The example that we were particularly interested in, in
2 our article, was use of electronic fetal monitoring. We're
3 working on that, whether clinicians sort of independently
4 believed that that was evidence-based and appropriate in that
5 situation or whether they did it because they were worried that
6 they going to get sued.

7 And so mostly it involved the use of emerging technologies
8 that the clinician didn't feel like necessarily was indicated
9 but wanted to do in prevention of a lawsuit.

10 DR. BLALOCK: And one more question. Dr. Spong.

11 DR. SPONG: Thank you so much. Cathy Spong.

12 I'm going to follow up again on the standard of care and
13 labeling, just because this is really circling for me to try to
14 understand. If the labeling isn't specific to pregnancy but is
15 specific for use in an adult, or an adult woman and she happens
16 to be pregnant, is that enough for the standard of care?

17 MS. SPECTOR-BAGDADY: Well, so this is all up to juries,
18 right. So what I say actually doesn't matter at all.

19 So, again, if the label is about the use of this drug in
20 an adult population, and there's no information that's
21 specifically relevant to pregnant women, the jury would
22 probably be even more likely to look at evidence of practice
23 rather than the label itself.

24 If the label were more specific and gave more information,
25 I think that this is what some of the clinician focus groups

1 were concerned about back in 1999, was that the more sort of
2 clinically directive information that's included in that label,
3 they were concerned that the higher the possibility was that
4 they would be sued for -- or not sued, because you can always
5 be sued, but they would be held liable for not following what
6 that exact label was.

7 So it's that constant tension in disclosure, that risk-
8 benefit analysis not only vis-à-vis the patient but vis-à-vis
9 the court system, vis-à-vis the jury, vis-à-vis Congress,
10 vis-à-vis those that are regulated. So that's why it's so
11 complicated.

12 DR. SPONG: Thank you. And is that risk of liability
13 increased for both the provider and industry, the manufacturer,
14 or separate?

15 MS. SPECTOR-BAGDADY: I'm sorry. So you're asking if the
16 risk --

17 DR. SPONG: The information on the label. If you have
18 more information on the label --

19 MS. SPECTOR-BAGDADY: Right. So that increases the risk
20 potentially for the clinician more so than the drug
21 manufacturer, because if you think of entities working in risk-
22 averse ways, in sort of ways to prevent litigation, drug
23 manufacturers are incentivized to disclose as much risk as
24 possible such that they can say our duty to warn the clinician
25 has been fulfilled. Then the clinician acts as the learned

1 intermediary who's supposed to adequately balance those risks
2 and benefits for the individual patient sitting in front of
3 her.

4 So I think that, ultimately, this is a problem for us all,
5 but it's a litigation problem mostly for the clinician.

6 DR. BLALOCK: Thank you very, very much.

7 And we'll now move on to our final speaker, Dr. Traci Lee.

8 DR. LEE: Thank you.

9 Good afternoon. When I saw on the agenda that I was at
10 the end of such an esteemed guest speaker list, it was a little
11 unnerving. But I hope to give you some insights on the
12 industry perspective, and we'll see how it goes.

13 Okay. So I've been -- so I'm a pharmacist by training.
14 I've been working in the industry for 20 years. I've been
15 working in labeling for about 12 years. And the reason I got
16 the job in labeling was actually the PLR, Physician Labeling
17 Rule, being announced in 2006. So thank you, FDA, for giving
18 me an opportunity to go work in labeling.

19 The other thing, I hope -- this is just one industry
20 perspective. I work in -- I've only worked in one company.
21 It's one woman's opinion. So we'll just go through kind of my
22 experiences on this.

23 Another thing I would like to say is I was talking to my
24 7-year-old that I was doing a talk on labeling. He's like,
25 mom, that sounds really boring. I think you need to try to

1 make them laugh. So this is my attempt to try to make you
2 laugh a little bit.

3 I will also say that I have a professional relationship
4 with GSK. I get financial holdings and my compensation as part
5 of my employment.

6 So as I mentioned, I wanted to give you one sponsor's view
7 on the regulation, how we approach the regulation in terms of
8 standardizing a process, the timelines, how we looked at the
9 data evaluation to make sure we were pulling the right risk
10 information in, also look at challenges, feedback we receive
11 from FDA, and also insights.

12 I'm not going to touch on this because we've talked about
13 the limitations of the categories in the earlier talks today.

14 Just in terms of the new regulation, when it was
15 announced, we initially gave feedback in 2008 on the draft
16 rule. And when we saw notification of the final rule in
17 December 2014, we were quite excited to have this framework, to
18 have these improvements in the labeling sections, to
19 communicate risks and benefits more effectively.

20 We really appreciated the fact that you had the synthesis
21 of data in the summary format, and also that it touched on
22 untreated disease states, which was not there before, and also
23 8.3, the addition of that section.

24 So it was quite overwhelming. We were excited but quite
25 overwhelmed by the amount of work that we needed to undertake

1 to execute this. What played into that was our extensive
2 product portfolio, so we started planning immediately.

3 So I was one of the labeling point persons assigned to
4 this from the beginning. And to start this, we had to consider
5 not only new products being written to meet PLLR but also look
6 at all of our established labels. And because GSK had
7 proactively converted a lot of our labels voluntarily into PLR
8 ahead of the regulation timelines, we had very few older
9 labels, and we knew that all of those PLR labels would require
10 a lot of work. So we started as soon as we could.

11 We created a cross-functional small PLLR sub-team that had
12 core members on it: labeling such as myself, a physician from
13 safety, Ph.D. from epidemiology, expert from non-clinical and
14 clinical pharmacology.

15 We met several times to define an internal process of who
16 would do what, who would contribute to what sections. We made
17 sure that management was in agreement with our proposal. We
18 had to gain safety board governance approval on our plan.

19 And then at that point, we went about creating briefing
20 materials, which included slide packs, broad email awareness
21 that we could send to all those disciplines within the company.
22 And then we would always -- the identified sub-team would be
23 the points of contact should anyone else in the company have a
24 question related to their discipline.

25 So I'm not going to go into too much detail on our

1 internal process here, but I just wanted to point out, on the
2 left column -- sorry. On the left column, these disciplines,
3 it was clear that each functional expert had an accountability
4 that aligned to what was expected to meet the regulation, in
5 terms of that section of the label.

6 So those folks went on an individual team. They were
7 assigned. They went away, did kind of their searching, their
8 review of the data, their evaluation, and kind of brought their
9 pieces together to the larger team, where we then looked at the
10 data presented in its totality.

11 And one other thing I wanted to point out on this slide is
12 prior to PLLR, we already had an internal safety panel, called
13 the Pregnancy Outcomes Advisory Panel, that's made up of
14 non-clinical and clinical experts, OB/GYNs, epidemiologists.

15 DR. BLALOCK: -- to speak louder.

16 DR. LEE: So this panel was already in existence. So we
17 took the opportunity, with all of these label updates, to take
18 the revisions, whether they be new labels or converted labels,
19 to this panel for input. So this was just kind of another
20 level of review that aided consistency. It allowed us to see
21 broad kind of differences across therapy areas and see what we
22 can learn from those different therapy areas.

23 I won't touch on -- sorry. I keep moving away. I won't
24 touch on this slide either, because we've talked about the
25 timelines over the 3 years, but what I will point out is I

1 mentioned we have a broad portfolio with more than 80 labels.
2 And when we looked at the timings for the June 2018, '19, and
3 '20, you can see the buckets of how our products fell.

4 That was going to be a lot of products' labels to get
5 revised in those, kind of the weeks or months leading up to
6 those time points. So what we had to do was change that, and
7 I'll talk about it on the next slide.

8 I also want to reiterate again that because most of our
9 labels were in PLR format, we expected significant changes to
10 occur. They would be submitted as prior approval supplements,
11 a lot of discussion with FDA. We had less than five that were
12 not in PLR format that would only require removing the
13 category.

14 And then just to mention one thing in terms of
15 Dr. Greene's comment earlier about Lamictal, so we have
16 Lamictal, and it's in this middle category, is due June 2019
17 based on its last approval efficacy supplement. But like I
18 said, we're trying to do them earlier, and Lamictal is actively
19 being worked on now. So while I don't disagree that the
20 labeling currently needs updating, we are actively working on
21 it as a sponsor.

22 So in terms of our timeline development, what we did,
23 instead of kind of targeting those 3-year time periods, we
24 assigned three to four labels to be updated every quarter.
25 That way we could manage the 80-plus. So what this resulted in

1 is earlier than the FDA implementation timelines. We do have
2 some that will still meet those timelines, but we just needed
3 to spread it out because of the resource.

4 Labeling itself, we identified the functional experts
5 within a given team or therapy area. We held kickoff meetings
6 well in advance of the regulatory timings or the timings that
7 we had set. And then we worked with each individual product
8 team to revise labeling to ensure we were in compliance with
9 the regulation and the guidance.

10 And I think it was Dr. Sahin's slide that talked about all
11 the discussions and reviews and really focusing on the risk
12 summary statements. It's very much similar in the sponsor
13 segment. Like in the industry, we spend a lot of time looking
14 at the data, summarizing it, and seeing what should be pulled
15 out into that risk summary statement before we submit to FDA.

16 Some of this stuff I touched on, but I guess what I want
17 to point out here is because it's so time consuming and it's
18 happening over several years, there's a lot of ongoing
19 education, because in industry, people move around on different
20 teams, and so while they may have gotten the initial training
21 or the initial blast of information, you're always getting new
22 people joining teams. So labeling really had to continually
23 provide education and training.

24 And then after we had a label revised or in a state that
25 we thought was ready, I would review the label as a single

1 labeling point of contact so I could share experiences across
2 different therapy areas, see what -- if there's anything I
3 learned on another therapy area that could be brought in.

4 Also, all of the members of labeling would review non-GSK
5 labels that had been approved so, you know, as months went by
6 and more experience was gained, we would look at that to see if
7 we could gain some experience with precedent language that FDA
8 had approved, and also the disease state risk language for
9 indications of interest.

10 So a really important thing about submissions, and I want
11 to make sure people are aware of this, is when you submit a
12 label to FDA, you have to support all the changes. And after
13 the first few submissions, it was really clear that we needed a
14 standardized supporting document template assigned to those
15 revised sections.

16 This would then include all the data supporting the label
17 changes, and also it gives FDA a real view of what we're basing
18 our risk summaries on. It also went over the search
19 strategies, the search strategies that we used for pregnancy,
20 the search strategies that we used for lactation, so they could
21 see what we're searching, compare it to their searches and see
22 did we miss any data.

23 So I don't have specific FDA feedback from this tool, but
24 it's worked internally well for us. And then another internal
25 feature is it gave clear accountability for the functional

1 experts on the sections they needed to contribute to.

2 We talked about the training. What I wanted to just
3 emphasize here is, again, the amount of time it took to do the
4 searches and also review the data, determine whether or not
5 that data, either internally or published, would come into the
6 label.

7 Also, you have these historical content in the label
8 that's already approved. Mapping out that historical content,
9 which could be decades old, really put our archiving systems to
10 the test. That was often difficult to find where some of that
11 came from.

12 And then when we brought the information, when different
13 functional experts brought the text to the team to discuss,
14 sometimes there was differing interpretations of the data
15 internally. And then anytime that changed, we had to always
16 assess, well, does this impact our global risk statement in
17 terms of our company core data sheet?

18 And then, of course, when we went to the FDA and we got
19 their initial comments back -- and someone alluded to that
20 negotiations with FDA, those can take several rounds. So we'll
21 submit something, FDA comes back. We'll submit something else.
22 It goes back and forth. So we had to come to resolution on
23 differing interpretations of data, what data should be
24 included, what shouldn't, like that.

25 In terms of standardization, we really tried to make our

1 searches standardized, and make our approach and our language
2 -- so you've talked about the intro language. We tried to
3 carry that through.

4 But as you know, there are, you know, about 16 different
5 review divisions that are reviewing these labels, and
6 oftentimes their preference or their differences and changes
7 come back to us. And so we're not forced, but essentially, we
8 need to go with the language that they recommend.

9 One thing I want to point out here: We talked about the
10 time consuming and all the meetings internally. I will say it
11 was a challenge for some of the older projects. Fewer
12 resources are assigned to those. So we just needed to ramp up
13 our resources for some of those, to make sure we had adequate
14 folks from multiple disciplines.

15 And then one thing I want to point out here is GSK did all
16 of our reviews, searches, reviews and writing internally. But
17 I know that several sponsors had to outsource this work. So
18 whether it was the searches themselves, the evaluation of the
19 data, or the writing of the text for the label, this probably
20 increases the complexity once you get to those negotiations
21 with the FDA. And this is presumably due to those companies
22 not having the expertise within, or just not the people to do
23 the work.

24 I'm going to skip that slide.

25 Okay. Other sponsor insights. We've talked a lot about

1 data and what's published and putting it in labeling, but it
2 was made very clear to us that not all data is appropriate for
3 labeling. It needs to be robust and well designed. And some
4 studies that we proposed were not accepted because different
5 methodology was expected by the various review divisions.

6 So that was a learning. We still generally proposed more
7 than less and let FDA come back and either take the information
8 out, but we wanted to make sure we were including as much as
9 possible that we thought was relevant.

10 We were able to align some of the labels with class
11 language. That's addressed in the guidance, and FDA has
12 approved that in some cases.

13 Across the different review divisions, I mentioned there's
14 different thresholds for including the data. Generally, we've
15 seen that limited information has been accepted in the clinical
16 considerations section, or it was streamlined and only the best
17 data was taken and kind of weaker data was excluded.

18 So I know that the Advisory Committee has questions that
19 you're asked to answer. We also just have some questions that
20 I wanted to put on this slide. Some of these align; some
21 don't. We've seen a lot of differences from the different
22 review divisions, and we haven't gotten a sense that a lot of
23 consultations are done for the Division of Pediatric and
24 Maternal Health. And we wanted to know if that would aid in
25 the review process, if they could be consulted more

1 consistently. It seems, in the few cases where they were
2 consulted, more relevant information seemed to be included in
3 the label.

4 And then we've talked a lot about data and how to present
5 data in there, what type of data. If there's any kind of
6 standards around inclusion data that can be created to guide
7 industry, I think that would be helpful, because we've
8 struggled with that, and again, there's differences across
9 review divisions that come back.

10 We've also been less successful in getting disease-
11 specific rates on, say, birth defects and miscarriage in there,
12 data not being robust enough to kind of compare to those
13 general background rates of birth defects and miscarriage. So
14 we wanted to know kind of what studies and what sources would
15 produce acceptable data for that.

16 This is my last slide. That flew by. So we defined and
17 agreed on a standard approach. We really had to focus on
18 timelines because of the 80 products and not putting in 40 and
19 50 labels in one month. I'm sure FDA appreciates us staggering
20 that as well because it is a lot of work on their part.

21 Updating labeling is a complicated process, and just in
22 terms of all the timings over years of how this has been
23 developed and the implementation timeline, it's not going to
24 happen overnight. It's going to take a while. But I feel like
25 we're making some serious progress in terms of getting

1 information out there.

2 We're trying to consistently apply the learnings we've
3 made. We're getting better at evaluating data and supporting
4 the data that we're including. I think my last point is
5 there's just not enough data, human data, that is. And I think
6 that we've all acknowledged that today. There needs to be more
7 information to help healthcare professionals make better
8 decisions.

9 So I will conclude there and take any questions.

10 DR. BLALOCK: Thank you very much.

11 Clarifying questions for Dr. Lee?

12 Dr. Berube.

13 DR. BERUBE: David Berube here.

14 I keep hearing calls for more data repeatedly, and I'm
15 concerned about two things. First thing I'm concerned about is
16 how do you -- how does the industry, as a sponsor, compensate
17 for the decline effect, which is a prominent effect in the
18 literature indicating that a vast majority of the studies that
19 have been published can't be replicated?

20 I mean, Amgen reported recently that they looked at 53
21 research papers and tried to reproduce the findings and failed
22 9 times out of 10. And the search for more data seems to be
23 challenged by this decline effect.

24 The second thing is I'm trying to figure out -- like
25 everybody's been talking about ways of approaching the subject

1 matter. You hit on it as well. Has anyone done like an
2 economic analysis on the desirability of investing limited
3 resources in producing a whole generation of new data when
4 we're not even convinced the new data's going to have a
5 significant impact on how carriers and pregnant women will
6 respond to the data?

7 DR. LEE: I mean, I don't know how to answer your
8 question. I mean, I think that in other areas in labeling and
9 getting labeling approved, there's data. So we're basing it on
10 data. I think that, you know, having more exposure information
11 would certainly provide us some more information.

12 DR. BERUBE: I did 2 years with the NSA on a grant to do
13 data triage, right. And the one thing I know about is what
14 happens when you have too much data. And I'm just, I just
15 don't see the utility of generating a whole new era of data
16 collection in the subject field until I am convinced that the
17 new data we're going to be generating is relevant.

18 And as we in risk communication know, the majority of
19 times it has nothing to do with the data, right. The messages
20 that you design that are effective or not have very little to
21 do with data. It has to do with a whole bunch of other things
22 that the public and even experts respond to.

23 And I just, I'm just wondering has anyone like taken a
24 step back and did this analysis, before we take a big step
25 forward and invest a whole bunch of resources to produce just

1 another set of data? Sorry.

2 DR. BLALOCK: And, you know, since that's a clarifying
3 question for the speaker, do you have a response or --

4 DR. LEE: I mean, generally, my feedback of wanting more
5 data comes from OB/GYNs, so that they can make decisions in
6 their patients. So maybe one of the FDA members who's, you
7 know, in that discipline could comment. That's what I hear is
8 that more data is needed, even with the individuals I work with
9 on these teams in the company.

10 We're only able to put in the label what data we have.
11 And if all those phrases, "inadequate," "not enough,"
12 "insufficient," "limited," if that's the first stance and that
13 doesn't help anyone, I'm just suggesting, what do we do?

14 DR. BLALOCK: Okay. And I think Dr. Yao wants to comment
15 as well.

16 DR. YAO: So if I'm hearing your question correctly, it is
17 whether or not we have evaluated the need to collect any
18 additional data at all, and whether or not those data would be
19 helpful in making informed decisions in the use of drugs in
20 pregnant women. If that's the question, then I would say
21 resoundingly that the answer is that we need more data. I
22 think that where we fall short, as we've heard, are in the
23 adequacy of the data that are available and the methodologies
24 that we use that give us more confidence.

25 So I don't think that the answer here would be that we

1 don't need more data. I think that the answer here is that we,
2 and in other spheres that are working on the collection of
3 clinically meaningful data in pregnancy and lactation, that you
4 know, there are actively other groups that are looking at that.
5 And I'm looking at Dr. Spong, too.

6 So that would be the first thing. The second thing I
7 would say that, you know, in this issue of reproducibility of
8 results and whether or not a study can be reproducible, I think
9 that's a slightly different question. And I think that
10 certainly at FDA, we have very strict regulatory standards that
11 are required in terms of both study design -- sorry, all three
12 areas, study design, study conduct, and reproducibility, and
13 the issue of relating to need for adequate and well-controlled
14 investigations, plural, to support an approval of a product.

15 So, in the regulatory space, I do feel like that we are
16 getting information. And we're asking for information that
17 will help us. In the area of pregnancy and lactation, I think
18 that we can all strive to get to that quality. And in the
19 meantime, we need to recognize the limitations that we have in
20 the data that are being collected currently.

21 DR. BLALOCK: Thank you.

22 Dr. Winterstein.

23 DR. WINTERSTEIN: Yes. There were two commentaries this
24 morning and now from you as well that talked about the lack of
25 standardization in expressing information. And you commented,

1 while you were transitioning to the new labels, on your efforts
2 to do so and the communication with the FDA, and there were
3 several review divisions and so on. And, of course, the FDA on
4 the other side has 18 or more manufacturers to work with, so
5 obviously that standardization can become very difficult.

6 So as new information -- could you comment on when new
7 information is emerging, what is your process of incorporating
8 that new information, along the lines of standardization and
9 keeping things up to date?

10 DR. LEE: So I thought that might come up because earlier
11 there was a comment about industry updating labeling.

12 So it depends on the lifecycle of the product. And when
13 they're newer, safety and pharmacovigilance, they're doing
14 reviews every 6 months. And when they're identifying flags or
15 risks, that gets progressed into the company core data sheet,
16 and then it's rolled out into local labels, which the U.S.
17 would be one of. When the products are older, I think it
18 expands to 1 year in terms of the review by the safety group.

19 So I'm not generating that data, being in labeling, which
20 is under the regulatory umbrella, but there are other
21 disciplines within the company that are evaluating that.

22 DR. WINTERSTEIN: Yeah. That would be the first data, so
23 the spontaneous adverse reaction data that you're talking
24 about. But, you know, obviously you have divisions in your
25 company that monitor any kind of safety information that

1 emerges around your drugs, and that could also be any type of
2 other Phase IV type of study. Is there a mechanism that this
3 information is reviewed and fed back somehow?

4 DR. LEE: My understanding is it includes published
5 literature as well. So when they're searching to do their
6 periodic safety update reports to give to health authorities,
7 they are looking at all aspects of safety.

8 I'm not in GCSP, the clinical global safety and
9 pharmacovigilance group, so I don't have a great knowledge of
10 that, but that's my understanding of how it works.

11 I see some nodding heads, so I --

12 DR. BLALOCK: Dr. Nahum, you had a question for the
13 speaker?

14 DR. NAHUM: Yeah. Actually it's a follow-up because I was
15 going to ask something along the same lines.

16 But one of the things I think, and I wonder what your
17 thoughts are on this, that is a little bit difficult, you just
18 outlined that there are periodic internal reviews that are done
19 at companies, and you said every 6 months or every year,
20 depending on the maturity of a product. I think in some cases
21 it's done more often than that.

22 But the question really always arises is when is new data
23 enough to change a label? And we heard a presentation this
24 morning, where with an antiepileptic product, the first data
25 that came in suggested that there was a very, very high

1 relative risk, associated with its exposure, for fetal
2 anomalies. And then later, as more data trickled in, it turned
3 out it wasn't nearly that much, if at all.

4 And so really what we need -- this is what I'm asking --
5 is do we need guidance from FDA to be able to say when is
6 enough of a change in the conclusion about safety data,
7 especially in a benefit-risk format, sufficient to go about
8 asking for a labeling change? And this is not something that's
9 trivial. We have to wrestle with it with every product that we
10 have.

11 DR. LEE: Was it to FDA or to me? It's a good point for
12 discussion. I mean, I do know that we have received --
13 sponsors receive information requests from FDA to make updates
14 and make changes to the label that they've identified that need
15 to be done.

16 I think it is hard to determine, like that critical point
17 where it's, like, okay, there's enough to change the risk-
18 benefit profile. But, hopefully, safety groups within industry
19 are evaluating that and they're looking at the totality of
20 data. And when they do their searches, they're adding them to
21 prior searches done. And when it gets to a certain level,
22 that's when they make a decision. And it's not just for a U.S.
23 label. It starts internally with a company core data sheet,
24 the position, and then, you know, expands from there.

25 I will say that this U.S. regulation, though, has prompted

1 those other discussions internally. And while some of the
2 background rates in the U.S. general population and the disease
3 state rates don't make it into our global core data sheet
4 because they're not relevant to other markets, we have
5 re-looked at information and gone back and updated our company
6 core position. So the U.S. is pushing us to like look at it.
7 And we've made updates because we found new data as a part of
8 adhering to the regulation, if that makes sense.

9 DR. BLALOCK: Dr. Pleasant, you have a question for
10 Dr. Lee?

11 DR. PLEASANT: Yes. Thank you.

12 All this, essentially a lot of this goes back to clinical
13 trial design. And so when you think about what the EU has done
14 on the summary requirements for clinical trials and how that
15 might create a feedback loop into the design of this trial, has
16 this labeling requirement started a similar parallel
17 conversation within industry when you look at the labeling
18 requirement and say, hmm, maybe we need to rethink the way
19 we're designing our clinical trials?

20 DR. LEE: Well, I think there's always an interest to do
21 that. The POAP panel that I mentioned, the Pregnancy Outcomes
22 Advisory Panel, they do inform teams of when it's appropriate
23 or not appropriate to include women of childbearing potential
24 and then what sort of precautionary methods need to be taken.

25 So I think that it's always being looked at, but maybe not

1 to the level it needs to be yet. I think it's a slow process.

2 DR. BLALOCK: And one final question for Dr. Lee from
3 Dr. Goldman.

4 DR. GOLDMAN: Yes. This is Myla Goldman. I actually had
5 more than one question written down, but I think maybe some of
6 them might be more clarifying for the whole group to couch
7 tomorrow's discussion.

8 But for you specifically, does GSK have -- it looks like
9 you have pregnancy registries for some of your products. Other
10 drugs that I'm familiar with have pregnancy registries. Can
11 you speak to is there any requirement or precedent in how that
12 data is reviewed and then reintegrated into the system? Are
13 you just collecting it? Is every company doing it differently,
14 because I would argue that we have all the data that we would
15 need to inform lots of these discussions, because as was
16 pointed out, we've been giving the flu vaccine to hundreds of
17 thousands of women for years, but we don't have any way to
18 harness that data.

19 So I'm curious, in this specific arena where we have all
20 of these pharmaceutical companies that have all these
21 registries, what's happening with that content?

22 DR. LEE: So I can't -- I don't recall all of the label
23 examples, but I know, for example, Imitrex for migraine, we
24 have enough exposures to sumatriptan that we have that
25 pregnancy registry data now approved in the PLLR format. But

1 there are other pregnancy registries where we didn't have
2 sufficient numbers of patients. And so we say there's limited
3 numbers to make conclusions.

4 The real -- I mean, my -- what I've observed -- go ahead.

5 DR. GOLDMAN: What's that cutoff? What decides sufficient
6 versus non-sufficient? Is that number available somewhere
7 or --

8 DR. LEE: Well, in our discussions, it's been like a
9 cutoff of around 300 and then 1,000 and then 3,000. Like
10 there's been various cutoffs, depending. But if it's less than
11 100, we haven't put it in.

12 So I think you have to look at the registry itself, make
13 sure they were all on a specific agent, and then determine if
14 it's appropriate to include. And then FDA then determines
15 whether or not they want to summarize that information there as
16 well, when we submit it to them.

17 So I don't have any hard and fast numbers, but that's just
18 coming to my head from like a general recall. We don't get as
19 many pregnancy registry entries or outcomes as we would like,
20 unfortunately.

21 DR. BLALOCK: And Dr. Spong has a very quick final
22 question.

23 DR. SPONG: Just point of clarification based on the
24 question from Dr. Pleasant. When you're updating these labels,
25 are you doing clinical trials in pregnant women to get that

1 information, or is this just based on what information is
2 available from registries?

3 DR. LEE: It's based on registries, published literature,
4 and then spontaneous reports that we have in our safety
5 database.

6 DR. SPONG: And do you routinely do -- does your industry
7 routinely include pregnant women in these clinical trials?

8 DR. LEE: We don't routinely. No.

9 One more question. He's got his hand up.

10 DR. BLALOCK: I want to move on to sort of the next. And
11 I see that Dr. Nahum has a question, so if we can get him first
12 on the list.

13 Thank you, Dr. Lee.

14 DR. LEE: Okay. Thank you.

15 DR. NAHUM: Yeah. I'm sorry.

16 DR. BLALOCK: But wait just a second. Wait just a second.

17 We're a little bit ahead of schedule, so we're going to
18 push things out of order just a little bit, push the break
19 down. We'll get it. We're not deleting it. But we'll just
20 push it down a little bit. And what we've actually got at
21 3:30, if you look at the agenda is another opportunity for
22 clarifying questions. And this broadens it up a little bit.

23 So as I understand it, we can ask, you know, clarifying
24 questions of any of the speakers this morning. So, again, they
25 should be clarifying questions, because we're very close to

1 being able to really open up the gates and have discussion, but
2 that will be after we get the charge from Ms. Duckhorn.

3 So clarifying questions for any of the speakers. And, you
4 know, if in the question, you can identify the speaker that
5 you'd like to address the question to, that would be great.
6 And then if that person can up to the podium so that they have
7 the mike, that would be great as well.

8 So, Dr. Nahum, thank you for your patience.

9 DR. NAHUM: Thank you. So Dr. Nahum.

10 One clarification on the last point that was made with the
11 last speaker: The one thing that I think might have been
12 inadvertently omitted is that there are Phase IV studies that
13 are collected often in parallel cohort fashion that also weigh
14 in to these types of ongoing safety assessments and benefit-
15 risk assessments. And I think that was just inadvertently
16 omitted, but maybe if the speaker could come back and clarify
17 that, that would be useful.

18 DR. LEE: I think Dr. Sahin talked about those earlier,
19 right. I don't have a lot of familiarity with those. We
20 haven't seen -- in the labels that I've worked on, I haven't
21 had results of those Phase IV studies described in that form or
22 fashion, but my understanding is they do exist.

23 DR. BLALOCK: Thank you.

24 Dr. Goldman.

25 DR. GOLDMAN: So I have two questions that maybe relate,

1 are appropriate for one of our FDA representatives.

2 One is Dr. Lee mentioned about disease-specific risk and
3 trying to find that. In that section of the labeling, who is
4 the onus on to provide that information about what is the
5 disease, the risk of the disease to pregnancy? Is it on the
6 industry sponsor, or is it on the FDA? Where does that
7 information come from?

8 DR. YAO: So, typically, we do ask the sponsor to provide
9 any information they have that would populate all of those
10 sections that apply. So we would ask the sponsor to provide
11 information. But as Dr. Lee had mentioned, FDA performs its
12 own independent review of the information that's available, to
13 make sure that we are more often than not coming to some
14 reasonable consistency about what those, you know,
15 disease-specific considerations are.

16 DR. GOLDMAN: Oh, can I ask my second question?

17 So my second question sort of ties into that, which has to
18 do with consistency.

19 So in several of the examples that were provided in the
20 background section, that the language was different, so the
21 details were the same, but the way the sentences were
22 structured were different from one label to another. And I
23 suspect, with this disease-specific, that also varies.

24 So is one of the discussion points to be around sort of
25 the opportunity for consistency, or is that one of the things

1 we're supposed to be thinking about for tomorrow?

2 DR. NGUYEN: That input actually would be very helpful to
3 us. I mean, we actually are very open-minded to suggestions
4 you may have to improve the information that we have,
5 acknowledging that the information we have is not the greatest
6 quality. So if there are consistent/standard statements that
7 you think will be helpful, we certainly would love to hear
8 that.

9 We would also like to, I think, make aware that we try to
10 fit these information under clean buckets, you know, I don't
11 know, inconsistent results, limited results. They do fit in a
12 bucket, but when you come down to each label, many times we
13 actually have to tweak it to really make it work for that
14 specific product.

15 As far as risk associated with specific diseases, I think
16 that's one area where we could gain consistency. So it really
17 varies on the different subsections of Section 8.

18 DR. BLALOCK: Dr. Dieckmann.

19 DR. DIECKMANN: Thank you. This is Nathan Dieckmann. My
20 question's for the FDA.

21 My head is spinning a little bit with just thinking about
22 all the risk communication work that could be applied to the
23 labels. And I keep coming back to trying to get clarification
24 on exactly what the goal of the labels are and whether the
25 intention is really to be a tool that would be used at point of

1 care.

2 So we've seen some examples of other web systems, TERIS
3 and so on, that if I was a busy practicing clinician, I would
4 certainly probably go to that TERIS system that showed me very
5 quickly the level of evidence that's available and whether that
6 risk can be estimated at all, as opposed to going to the label.

7 But we've also learned there's a lot of other legal
8 requirements that should be communicated. So I guess I'm
9 looking for, as we're all going to go down the rabbit hole soon
10 in giving you like recommendations on exactly how to change the
11 labels around, just more clarification on exactly what the
12 goals are or maybe a range of the different uses, just to kind
13 of help target our recommendations.

14 DR. NGUYEN: Thank you for those questions. I think
15 they're really important questions.

16 So your first question is, is the labeling intended to be
17 used by prescribers at point of care? We hope so, but we also
18 understand it is a relatively cumbersome tool for a busy
19 practitioner. But we certainly would hope that would be a
20 popular source, so to speak.

21 Certainly, that's why the PLR and now the PLLR changes
22 were done, so to make it more useful to prescribers. That's
23 why we have the half-page highlights summary. So that answer
24 is yes, we do intend it to be used at the point of care.

25 The second thing that I will mention is that we certainly

1 are aware of many other sources of information that's easier to
2 use that gets you sort of like the end game statement, but
3 recognize that a lot of those sources actually get their
4 original information from the prescribing information. And
5 they might modify it for certain types of prescribers and what
6 have you.

7 And, thirdly, the prescribing information is not intended
8 to be clinical guidelines. So I think that's where its
9 limitation, so to speak, is to a practicing clinician, because
10 clinicians like set guidelines. And that's why we have
11 professional societies weigh in and what have you, but they too
12 rely on information that's in the prescribing information.

13 DR. BLALOCK: Dr. Lyerly.

14 DR. LYERLY: Thank you. I just wanted to follow up on
15 Dr. Spong's question to Dr. Lee.

16 So in your trials with women of childbearing potential,
17 obviously there are going to be some inadvertent pregnancies
18 which are sometimes relied heavily on as a source of data for
19 the safety of drugs and vaccines in pregnancy. And I was just
20 wondering if you are collecting those data, and maybe for the
21 FDA, if there is some avenue for those data on inadvertent
22 exposures in trials to get to the label.

23 DR. LEE: So we are collecting those data, but I think
24 what typically happens is drug therapy is stopped after the
25 exposure. But we collect those data, and they become a part of

1 our internal safety databases. But if they're not sufficient
2 quantity, so it's a handful, it's not moving into the label
3 because it's not enough to be helpful. But the outcomes or the
4 follow-ups are collected.

5 DR. LYERLY: So when you offered the numbers for the
6 registry, sort of thresholds, do you have different thresholds
7 for inadvertent exposures that you deem relevant, or how do you
8 think about that?

9 DR. LEE: Well, because the inadvertent exposures aren't
10 intended and they're inadvertent, I don't think that we are
11 hoping to get those and collecting it to a certain number. But
12 I would suspect that if you got hundreds or thousands, it would
13 be a similar approach. But I don't think it happens because of
14 the pregnancy prevention guidelines that we put in place.

15 So the numbers that I quoted were more for pregnancy
16 registry once it's approved, out on the market, and you're
17 collecting those outcomes.

18 DR. LYERLY: Okay. Thank you.

19 DR. BLALOCK: Dr. Coombs.

20 DR. COOMBS: Yeah. I want to go back to earlier today
21 with Dr. Namazy.

22 When you were talking about the information from the
23 physicians and their reactions, kind of in the results and the
24 values section, did you say something along the lines that this
25 did lead to more discussion of risk and benefits with the

1 patient, with this new type of labeling?

2 DR. NAMAZY: No, no. What I -- sorry. I didn't have that
3 part on the slide. I kind of mentioned it at the end of the
4 slide. But I think that was talking about when we asked the
5 responders, based on reading, after reading the narrative
6 summary, would you use drug ABC? Fifty-three, I think it was
7 53% said that they would, or that they would use it but they
8 would have to really consider the risk-benefit.

9 DR. COOMBS: Okay.

10 DR. NAMAZY: So there were a lot of comments just kind of
11 talking about risk-benefit with the patient. And that just
12 kept coming up, so that's what I wanted to put out there.

13 DR. BLALOCK: Dr. Lee.

14 DR. LEE: Two quick questions for the FDA folks; one is a
15 follow-up to Dr. Goldman's question about standardizing
16 phrases. When the sponsor edits the label, do you guys, are
17 you guys able to just go ahead and edit as you wish, or does it
18 have to go back to the sponsor?

19 DR. NGUYEN: So, in most circumstances, there's certainly
20 a limited number of circumstances where we, quote/unquote,
21 "dictate" the language. But in most instances, it's actually
22 negotiations back and forth, with the final language being
23 approved by FDA. But certainly during that, during those
24 negotiations, FDA does provide its own edits and there is
25 rationale provided.

1 DR. LEE: Okay. And the second quick question is have you
2 thought about pulling out some of the absolute risk information
3 into a separate, searchable database form outside the narrative
4 so that, you know, technology companies can leverage that to
5 represent information graphically and compare it against
6 baseline? So is there a thought about how that could be made
7 available?

8 DR. NGUYEN: So I think this goes back to why we need more
9 data. Data is a four-letter word, so it could be good or bad.
10 But, certainly, what we strive to have is reliable data. So we
11 would not want to publish, be it relative risk, absolutely risk
12 numbers, unless we felt some level of confidence in those
13 numbers, and our state of science right now is that we're not
14 very confident in most of those numbers.

15 So we would love to be able to generate a database like
16 that, but the information populating that database is missing.

17 DR. YAO: Just to add onto Dr. Nguyen's comments, and I
18 think Professor Conover said it very nicely too, which is that,
19 you know, her patients or her or the prescribers that go to her
20 for advice are saying, come on, just tell me what the code is.

21 So we have been very, very conscious of the fact that we
22 want to provide standardization when we can and want to
23 describe the nuance that we can, but we don't want to create
24 just another lexicon that anything FDA says this, that just
25 means A, anything FDA says that, it just means B. So that's

1 the part that's hard, and that's kind of the part where we'd
2 like to get more conversation tomorrow.

3 DR. BLALOCK: Ms. Robotti.

4 MS. ROBOTTI: Thank you. I guess this is for the FDA.

5 The package insert that -- the information that we're
6 talking about today is really targeted towards the physician.
7 Where is the patient supposed to get their information from?
8 They take the ultimate risk and hope for the ultimate benefit.
9 But it's written in language you cannot expect them to
10 understand.

11 DR. NGUYEN: So as we mentioned a little earlier this
12 morning, many prescribing information comes with a medication
13 guide, which is really written for the patient. And the
14 patient would typically receive this when she receives her
15 prescription. Or another documents that might accompany the
16 prescribing information is what's called a patient information
17 leaflet. So that's really sort of part of FDA-approved
18 labeling, and those documents are written for the patient.

19 Now, the second component, and this is really important,
20 is that the patient has her physician to counsel her, and there
21 is expectation that there'll be counseling between the patient
22 and the physician. So that's sort of the regulatory paradigm
23 of prescription drugs. It doesn't explain the universe of
24 information where the patient gets her information.

25 MS. ROBOTTI: And so the medication guides, is the

1 phrasing used within those guides, is that within the purview
2 of this Panel today?

3 DR. NGUYEN: It is. So the medication guide is actually
4 part of FDA-approved labeling. So in the most sort of concise
5 way, you have the prescribing information, and it would have a
6 medication guide accompanying the prescribing information. And
7 those are all -- they have to be FDA approved.

8 DR. YAO: Can I just clarify, ask the question? Are you
9 asking if what we're asking advice on, as part of this Advisory
10 Committee, what you want us to be able to tell patients?

11 MS. ROBOTTI: Yeah.

12 DR. YAO: So I guess the short answer would be not so
13 much. I mean, we do in the context of wherever you think it
14 might be important in the PI, for example, if you have specific
15 comments about medication guide. But we really, we've got a
16 big task in front of us, the rest of today and tomorrow to talk
17 about what we're putting in prescriber information. So that's
18 really what we want the Committee to focus on.

19 DR. BLALOCK: Dr. Rimal.

20 DR. RIMAL: Thank you. I actually had another question,
21 but I wanted to follow up with what was just said.

22 The patient information leaflet, the patient has access to
23 that only if she's given the -- she decides to take the
24 medication prescription, right. Otherwise, there's no other
25 way for her to get that information.

1 DR. NGUYEN: Yeah. Actually, if you go to certain
2 searchable databases -- FDA's is Drugs@FDA -- you should have
3 accessed to FDA-approved labeling. And often you'll see the
4 medication guide or the patient information leaflet with that
5 information.

6 And, actually, while I'm at it, I will clarify that the
7 documents that are for the patient contains the information
8 that's in the prescribing information. It's written in
9 patient-friendly language, but it certainly contains the
10 information that's most important for the patient to safely and
11 effectively use a drug.

12 DR. YAO: We would be happy, if the Committee would like,
13 during the break to pull up an example or two of what that
14 looks like.

15 DR. RIMAL: If you don't mind. So I'm reflecting back on
16 the conversation we had this morning about how to effectively
17 communicate risk information. And much of that focused on the
18 presentation format, you know; do we talk about the numerator,
19 the denominator, percentages, etc., etc.

20 To me, what was missing from that discussion was anything
21 to do with the receiver characteristics of that information.
22 So we know, for example, there's a whole group of people in
23 this country who feel very disenfranchised, whose trust towards
24 the medical system is very low and therefore are not likely to
25 receive that information in -- or they're likely to receive the

1 information in a certain light.

2 So when we talk about labeling, I have some discomfort
3 with the fact that we're focusing exclusively on the language
4 and how it is framed. And there is nothing there about the
5 patient himself or herself. And, you know, I think it's a
6 tension between, on the one hand, standardization of the
7 information we provide, which many people have talked about,
8 and on the other hand, personalization of that information so
9 that it's palatable to the particular person you're targeting.

10 So I guess there's a broader question to the FDA in terms
11 of our charge, and I guess to Jodi, before we get that charge,
12 is there any room for having some recommendation for at least
13 understanding some aspect of the patient as a requirement in
14 the language that we present?

15 DR. NGUYEN: So I think you hit on a really good point of
16 the limitations of what we can do with the prescribing
17 information. And I know it sounds like we're very focused on a
18 document, but certainly its intention is to contain all the
19 information that will assure the safe and effective use of a
20 drug. It is information. It is for the general audience
21 consumption. It is certainly not designed to able to
22 individualize to a certain patient based on her unique
23 risk-benefit balance.

24 And so I think I just want to be very clear that this is
25 what I like to call a general information document. And then

1 you have the prescriber, who's going to help translate that for
2 the individual woman and have that dialogue with her and
3 incorporate her values, you know, her risk tolerance and what
4 have you. So that really is done on that patient-prescriber
5 relationship side.

6 So I hope that helps clarify the limits of what we can do
7 with prescribing information.

8 DR. BLALOCK: Dr. Spong.

9 DR. SPONG: Thank you.

10 My comment, clarifying question is really to Dr. Wisner
11 and maybe a little bit to Dr. Riley, and it flows directly from
12 this conversation we're having.

13 Dr. Wisner provided a wonderful example of how she
14 counsels patients and how she takes information, and is looking
15 at both the condition that the patient has as well as the
16 medication that might be useful and that whole counseling
17 around that description.

18 And I guess I'd like to have a little clarification from
19 her of, you know, how long does that take? How is she able to
20 do that, knowing when I see a patient, I don't have, I think,
21 enough time to be able to get done what's describing in the
22 current confines of how they're set up. And how might what we
23 provide in this document be able to assist that, so as to allow
24 us to be able to give that information in the time constraint
25 environment in which we live?

1 DR. WISNER: Yeah. It's a good question. In the
2 environment I work in, which is an academic, psychiatric
3 consultation service, it usually takes me about 45 minutes to
4 an hour to do an assessment like that. And it potentially
5 could take longer, except that I do some of what I was talking
6 about in the presentation as well, which is I look through her
7 medical record and I get information on the new drugs I'm not
8 entirely familiar with and I get all my materials that I'm
9 going to hand out in advance.

10 So it does take a fair amount of preparation. So, yeah,
11 it takes a while. How could it be shorter? Well, I keep
12 thinking again about this New York model where you have all
13 that information in advance and somebody else pulls together
14 the information for you, because it really helps to have some
15 sense of the information about a particular drug and disease in
16 hand before you go talk to the patient, because it helps focus
17 your questions for the patient and the assessment of her
18 disease state as well.

19 Sometimes, if I have a real limited amount of time, what
20 I'll do is do the assessment and set up a series of questions
21 that we'll answer in a phone call later. And sometimes that's
22 necessary because the patient has a lot of decisional conflict
23 and can't really make a choice at that time and wants to talk
24 to her significant others. So you're right, it is time
25 consuming.

1 DR. BLALOCK: Dr. Yao, you have a response as well?

2 DR. YAO: I do. And I think, just to clarify and to ask
3 the Committee to think about it as we move forward into our
4 discussion questions tomorrow, on my Slide 6, if you want to
5 take a look at that again, that slide says that the labeling is
6 for a summary of essential scientific information needed for
7 the safe and effective use of the drug that is written for the
8 healthcare provider, that it must be informative, accurate, and
9 neither promotional in tone nor false or misleading, and it
10 must be updated when new information become available.

11 So that's sort of the low bar, right. That's the minimum
12 that labeling should achieve. However, having said that, in
13 any way that the labeling can be improved such that it's a
14 better tool when you're busy and there's little time, or that
15 you are coming up against cultural, you know, longstanding
16 societal issues that you think this document could be improved
17 upon, that's exactly the kind of advice we're looking for.

18 DR. BLALOCK: Dr. Kreps.

19 DR. KREPS: You know, I've been listening to the
20 conversation all day, and I'm -- you know, this is something
21 that I'm kind of confused about, so I'm hoping that my friends
22 from the FDA, Christine and Lynne, can help me with.

23 It seems that you want a clarification on how to develop
24 the labeling message, but I'm not sure if it's clear what the
25 information is that you want to present. So we've heard this,

1 you know, common phrase about we need more data, but it sounds
2 like the data that you currently have is equivocal. It's hard
3 to understand, and it's not consistent.

4 And I wonder if there's a -- you may already be doing
5 this, but I wonder if there's kind of a review to evaluate what
6 are the strengths of the data, what do we know, what do we
7 don't know, and what are the conclusions that we can reach?
8 It's extremely difficult to come up with a good message when
9 you're not sure what it is that you want to present.

10 And it sounds like, from some of the sample messages,
11 label messages, the messages themselves are confusing because
12 they're not clear recommendations. And so maybe, you know, a
13 step before, you know, standardizing the labels would be to
14 step back and say how do we clarify what it is that we know?
15 And what are the lessons learned? What do we want to recommend
16 in terms of the strength of the evidence? And how do we
17 clarify that? Because once you have a clearer sense of what it
18 is you want to communicate, then I think it becomes much easier
19 to develop a really good set of messages. But without that
20 information, it's very challenging.

21 DR. BLALOCK: Dr. Goldman.

22 DR. GOLDMAN: My question was related to the -- for the
23 FDA. How does this work, then, for generics and biosimilars
24 where, you know -- just as a point of understanding, do they
25 carry the original label, or how does that happen?

1 DR. YAO: Right. So, for generics, that's a pretty easy
2 answer. Generics that are prescription fall under the same
3 requirements under PLLR. So the reference product labeling, if
4 that's an NDA, which is, you know, our regulatory term, if
5 there's a drug that's still a holder of the labeling, all the
6 generics will be required to fall after that.

7 And if it's a generic that's the reference product, they
8 have to change their labeling, and then all the generics have
9 to go. For biologics and biosimilars, it's the same. Anything
10 that's prescription product falls under PLLR if it was approved
11 after 2001, and then some of the other rules that we talked
12 about.

13 DR. GOLDMAN: What I mean is does each individual
14 pharmacologic entity need its own PI?

15 DR. YAO: So they all do, and generics follow very
16 closely. They have to contain the same labeling as the
17 reference product. So that's fairly easy to convert. I should
18 say easy -- I'm not -- I don't work in generics, so I'm sure
19 it's not that easy. But, you know, all of those labelings have
20 to --

21 DR. GOLDMAN: The manufacturer of that generic is also
22 submitting the PI.

23 DR. YAO: No, they are not, generally not. They will
24 follow whatever reference product has submitted their labeling
25 change.

1 DR. GOLDMAN: Got it.

2 DR. YAO: And then all the -- then the generics have to
3 change their labeling to be the same. There's no negotiation
4 there really.

5 Biosimilars are slightly different, but we haven't gotten
6 to the point where we have -- you know, the biosimilars were
7 negotiating those new labelings anyway, so --

8 DR. KREPS: Re-address, I get the --

9 DR. BLALOCK: Sure. And -- but make the, you know, make
10 the question, you know --

11 DR. KREPS: All right. So the --

12 DR. BLALOCK: Clarify what the question is.

13 DR. KREPS: The question I had was basically about data
14 reduction. Is there a need to try and clarify what it is you
15 want to say, and is there a method for doing that?

16 DR. NGUYEN: So if I think -- if I may rephrase your
17 question and make sure we can answer it for you, is that
18 present -- in the present, we have data/information that's very
19 nebulous. You know, you can tell by a labeling there's a lot
20 of, well, it shows this, we kind of don't know, and you know,
21 that's all we can say, right.

22 We're not saying don't take it, take it, take it with
23 caution, or anything. And your question is given that
24 circumstance, FDA go back, figure out what you want to say
25 based on your review of the information and figure that out,

1 and then perhaps we can help you. Am I understanding that
2 correctly?

3 DR. KREPS: Yeah. I'm basically saying, figure out, you
4 know, where the findings are relatively clear. There are some
5 cases, I'm sure there are, that you have some clear evidence,
6 but there are probably many where they're not. So identify
7 where you have the strongest evidence and put that in a group
8 where you're ready to go for messages.

9 Identify the ones where the messages are not clear. You
10 may need to clarify and follow up and then direct that type of
11 effort to get better information. Because the better the
12 findings are, the stronger the findings are, the better able
13 you will be to come up with meaningful labels.

14 And so, you know, maybe this is not the case. Maybe all
15 the information is clear and that's not the problem, but that's
16 not what I've been hearing.

17 DR. NGUYEN: So I think the bad news is that we don't have
18 clear information. So the labeling that you see is the best
19 that we could do right now. We combed through multiple sources
20 of data. We threw out information that we thought, well, you
21 know, really, we're not going to include that in labeling. And
22 believe it or not, the information we put in labeling is what
23 is the best available.

24 And what we're struggling, and that's why we're having
25 this panel today is, is this helpful in any way? We have to

1 put in best available information. The law requires that we do
2 it. We can't wait until we have clear data before we put it in
3 the labeling. So given our current conundrum and situation,
4 how do we best do it?

5 So you're confused, and I think it reflects, you know, the
6 struggles that we have on this end. And so we're trying to get
7 your input in terms of how we can best do this, given the very
8 imperfect situation that we're in.

9 DR. BLALOCK: And it looks like Dr. Yao wants to respond,
10 but I also want to comment that actually what I'm hearing more
11 is a recommendation from you rather than a question. And we're
12 going to have lots of time for that, but I also have a sense of
13 maybe moving on to clarifying questions.

14 But, Dr. Yao, it looks like you're jumping, wanting to
15 respond.

16 DR. YAO: Yeah. I just want to say one thing, which I
17 agree actually, Dr. Blalock, completely with what you've just
18 said. And I just want to remind the Panelists, because we've
19 got, you know, just the tenor of the conversations, the
20 questions that are being asked already give me great hope that
21 we're going to have a very important outcome from this meeting,
22 which are recommendations that will help us.

23 But to your point, Dr. Kreps, what we have -- what we had
24 historically in labeling is more or less exactly the same as
25 what we have now, except for we removed that letter. And now

1 everybody thinks that everything has been changed.

2 The effort that we've been making is to provide more
3 information because we felt like the letters were not doing the
4 trick. And we had lots and lots of advice and input previously
5 that said these letters weren't really telling the full story.

6 So as we're moving away from that, we've been trying to do
7 our best to describe these nuances, to describe the
8 inconsistencies when we've had them, the conflicting
9 information when we've had it, and then the lack of information
10 when we've had it, and in the very, very rare circumstance
11 where it's been more or less easy, when we had a clear signal
12 that was easy to write and that people knew.

13 So what we're trying to do is construct a way -- we've
14 constructed some examples that we'll go over and discuss again
15 tomorrow, but to get your advice about how do you describe
16 that, those nuances in a way that doesn't need to another
17 letter categorization and that we hope fills that void that
18 prescribers want, which is this perception that those letters
19 were helping us.

20 DR. BLALOCK: And I've got, you know, quite a long list of
21 folks who have questions, and I think we're going to have time
22 for, to get around. But just again, you know, asking for
23 everyone to keep them to, you know, short clarifying questions,
24 and then we'll get to discussion and recommendation very soon.

25 So the next person on my list is Dr. Wolf.

1 DR. WOLF: And I think I don't want to repeat too much
2 about -- Gary, I completely feel your pain, and I feel yours.

3 The question, I guess, is what is your outcome? Is your
4 outcome -- and this is what I've been wrestling with, and if
5 it's denied, but is the outcome that you're dealing with
6 prescribers who have to deal with treatment uncertainty, which
7 I get, because you're not going to answer it until the data
8 comes in?

9 And I actually do agree with everything you said. You
10 need more data. Yes, it's a good or bad word, whatever you
11 want to get into. But are you looking to see, to kind of
12 either assist prescribers in getting through that uncertainty
13 because it's not going to go away?

14 And if that's the issue, versus just the messaging, I just
15 want to make sure that I understand. This is a true clarifying
16 question. If our job, as this Committee, is to figure out how
17 best to convey in a manner the uncertainty around the data that
18 we have as to what to move forward with, because you're not
19 looking to see -- based on the evidence, you don't have the --
20 to know with any specific patient that they did the right thing
21 or not in that particular case. Is that -- you're just trying
22 to make sure that you can convey, as best as possible, we don't
23 know?

24 And the next level would be -- and I didn't know, with the
25 PLLR -- I'm more familiar with the PI -- that you had, since

1 2006, you had guidance that would include patient counseling.
2 I think that's when it first kicked in that you were supposed
3 to provide some guidance that I don't think probably many
4 prescribers use, mostly because there's kind of a disconnect
5 between how that material actually gets into the flow of
6 patient care that Dr. Dieckmann kind of raised.

7 But is that also part of it? Is there opportunity that
8 you also are trying to figure out how to not only address the
9 reconciliation of the uncertainty but also how they might
10 communicate that to patients? Does that make sense? Because
11 that used to be part of the PI.

12 And I don't know if that -- there used to be some section
13 that was supposed to provide some words, you know, based on all
14 this stuff on clinical trials, what you've learned, animal,
15 whatever you want to get into, that boil it down, these are the
16 three or four things you should tell patients when you're
17 ordering this med.

18 DR. NGUYEN: So I'll apologize. I'll clarify that. So
19 the PLLR is actually a part of PLR; it just -- it's been
20 delayed intentionally for that gap. So to answer your
21 question, yes, we would really like to hear your input on how
22 we can present the information in pregnancy in a way that can
23 be interpreted by the prescribers. We are not removing
24 uncertainties because they are what they are. You have a black
25 sheep, you have a black sheep. You're not going to remove the

1 blackness of it.

2 So yes, how do we best communicate uncertainties in the
3 way that really can be translated by prescribers so that they
4 can use the information, as opposed to reading it and saying, I
5 have no idea what confounders mean, for example.

6 We are also looking for input so that we can give
7 information away that doesn't tie a prescriber's hand. So we
8 hear a lot about, you know, don't be too prescriptive, FDA,
9 because you tie our hands. We may have a patient or two who
10 really needs this. So we like to make sure we're not doing
11 that under appropriate circumstances. Now, if they're clear
12 risks, we're going to communicate that they're clear risks. So
13 that's the second part of it.

14 As far as the patient counseling section I think that
15 you're referring to, it's the last section that's in the PI,
16 yes. So there are some regulations that dictate what we put in
17 the patient counseling information. And if the pregnancy-
18 related information meets the criteria to put it in patient
19 counseling, we will put it in there.

20 But, again, if you have pretty neutral risk information in
21 a pregnancy, that's not something we're going to carry over
22 into Section 17. Section 17 is a little more what I call
23 active counseling. For example, the patient needs to avoid
24 certain medications, if she has to take it with food, if she --
25 you know, if there's active counseling that must be done, then

1 that's usually included in Section 17, but not everything.

2 There are criteria that dictates what we put in there.

3 DR. WOLF: Just to clarify, so you wouldn't -- this is
4 helpful to know. So you would not put information in this, in
5 the instance, in patient counseling section, on how to explain
6 to a patient why they shouldn't be on this medication if -- or
7 if you chose to, we're going to proceed, but we don't know?

8 DR. YAO: So, generally, the patient counseling section
9 includes information that has been described in other sections
10 of labeling to the prescriber that are -- that we want to make
11 sure the prescriber communicates. So those usually land in the
12 area of warnings and precautions, do not use -- you know,
13 advise the patient to use contraception, those kinds of things,
14 which don't lend themselves to the conversation of what we want
15 to put in 8.1 when we're not sure what the risk really is.

16 So I would say then, in general, that kind of conversation
17 would likely be limited to Section 8.1 and not necessarily, you
18 know, bleed if you will into Section 17, because it might sort
19 of change the important messaging we want to get across in 17.
20 Does that make sense?

21 DR. BLALOCK: Dr. Joniak-Grant.

22 DR. JONIAK-GRANT: Dr. Joniak-Grant. I had a question.

23 The goal here is that we want the labels to work better
24 and to be used by the healthcare provider, right? And,
25 Dr. Namazy, correct me if I'm wrong, but you -- I believe that

1 you intimated that the providers were more likely to use the
2 label if they felt it would be -- was in a sort of patient-
3 friendly format, easy to digest, they could get through it on a
4 busy day and sort of move on.

5 DR. NAMAZY: Well, the question didn't get that specific.
6 Basically, the question was do you use the pregnancy labeling
7 system, pregnancy label to make decisions? And 73% said yes,
8 but there was, you know, other outlets where clinicians do
9 look, such as UpToDate and Lexicomp, other places that we had
10 said. But 73% said that they do use the label when deciding to
11 use a medication.

12 DR. JONIAK-GRANT: Because I guess I was looking at the
13 slide that said what's next --

14 DR. NAMAZY: Oh. Will you pull that one up?

15 DR. JONIAK-GRANT: -- which suggested that many clinicians
16 lack the time to navigate through information and present it in
17 a clear way to their patients. So would having a label be
18 written in a clear way for patients help deal with this issue?

19 DR. NAMAZY: Absolutely. Twenty-nine percent and forty-
20 nine percent didn't think that it was clear or concise. So
21 that lends you to believe that maybe it needs to be a little
22 bit more clear and concise. I think that's why I put that last
23 statement in.

24 DR. JONIAK-GRANT: Okay. Thank you. And then with that,
25 I guess I don't see why that's sort of counterintuitive to be

1 mindful of what would help, what would be patient-friendly
2 speech. I feel like it's sort of being presented as healthcare
3 provider world, patient provider world, rather than, well, if
4 we made it friendlier for patients, we're also making it
5 friendlier for the healthcare providers.

6 And along with that, sort of this notion that -- this
7 notion that patients can just go ask their doctor is -- I think
8 really doesn't recognize that everybody has access in a timely
9 way or financially. The medication guide generally has very
10 little information that's useful for anything more than, you
11 know, how many times a day should I take it, do I take it with
12 food or not?

13 And so I guess I see the benefit of putting it in patient-
14 friendly terms on all these things. I don't see where there's
15 not a benefit. And so I'm just kind of puzzled why there's
16 such this strong bifurcation.

17 DR. YAO: Yeah. If I could use an example to help maybe
18 describe what the difference is, which I understand exactly
19 what you're trying to say. And please don't take that what
20 we're saying is that because the labeling is intended for the
21 prescriber, that we don't want it as clear as possible for the
22 patient.

23 But if we take the example -- and I think this might
24 help -- of the difference between labeling in a prescription
25 product, which we, you know, understand under, you know, law

1 that a prescriber that is licensed to practice in whatever
2 jurisdiction is the one that must write for that drug, right,
3 versus something that appears over the counter.

4 So over-the-counter labeling is a very different beast
5 than prescription product labeling, and I would, you know,
6 point you to the drug facts label, which is the title that we
7 give to over-the-counter labeling, which very much is
8 absolutely intended for the consumer.

9 And that type of labeling is fundamentally written in a
10 different way than what is written for prescription product
11 labeling. So that gives you, I think, a flavor of what we mean
12 in terms of the difference.

13 Having said that though, again, I appreciate your point,
14 and we're not saying that we don't want information that's, you
15 know -- that can be unclear and imprecise, because we're going
16 to give it to prescribers who must understand this all and then
17 can translate it to, you know, patients.

18 We understand that patients are going to read this
19 information too, so we do want it -- we also understand that
20 the information that's taken from labeling, prescription
21 product labeling, often gets turned into -- right, digested in
22 some way and then turned into information that patients will
23 read directly. So we want to make sure it's as clear as
24 possible so that translation doesn't get messed up either.

25 DR. BLALOCK: Dr. Berube.

1 DR. BERUBE: This is for you, for the FDA. Dr. Berube
2 here.

3 Now that I know that the primary audience we're dealing
4 with is prescribers, then all this innumeracy thing confused
5 the hell out of me because prescribers should be able to do
6 basic counting, right. I mean they're mathematically
7 competent. So I'm not concerned that -- well, more than the
8 general public, all right.

9 The reality is that these experts have other problems;
10 they have other heuristic problems. There's this thing called
11 the egocentric bias, where if you tell them too much, they back
12 off, right. And you mentioned that to us. There's the other
13 bias, which is the risk-averse bias, which is that they want
14 you to tell them, with incredible clarity, what the risk is.

15 Tell me if I'm heading in the right direction. You want
16 us to help you find the sweet spot between the ego-aversiveness
17 where you're telling them too much and the risk-aversiveness
18 where you're not telling them enough. Is that where we're
19 heading?

20 DR. YAO: I think those are all very valid points in what
21 we might want to discuss tomorrow about when we have a
22 statement that, understand FDA, that that may make the
23 prescriber who is risk-averse or the patient who's risk-averse
24 not -- what is that consequence for including it this way?

25 So yes. That's the kind of information we'd like to hear,

1 but I'm not sure that in any case, you know, we're going to
2 get -- that there is a, you know, sweet spot for all drugs, for
3 every indication, for every patient and for every provider.

4 DR. BERUBE: You're probably correct.

5 DR. BLALOCK: Dr. Sneed.

6 DR. SNEED: I think it's pretty much been covered, but in
7 your Slide 6, you talk about healthcare provider, and then you
8 talk about prescriber. Is that meant to be the same thing?

9 DR. YAO: Thank you for the clarification. So, you know,
10 we know that prescribers now, you know, are not just
11 physicians, and some healthcare providers aren't prescribers,
12 but we're really talking about prescribers.

13 DR. SNEED: Okay. So it sounds like, to me, that the
14 purpose of this is to help a prescriber decide whether that
15 medication is appropriate for this pregnant or lactating woman,
16 because then if you're talking about the whole counseling
17 thing, then they may not be getting the counseling from that
18 prescriber because most prescribers don't have 45 minutes.

19 And then, also, there's the intimidation factor that
20 people feel around doctors. And so they may ask their
21 pharmacist, or they may ask the nurse or someone else for
22 information, for clarification. So it seems like there are
23 multiple audiences going on.

24 DR. BLALOCK: Dr. Tracy.

25 DR. TRACY: Jim Tracy. I'm still also kind of wrapping my

1 head around this labeling thing too, a little bit, and part of
2 what our charge here is going to be.

3 You know, we've spent a lot of time talking about
4 communication of risk of using something. And it's been
5 touched on by several of our speakers. And I keep getting kind
6 of consumed by the risk of not doing something sometimes.
7 We've touched on that. And I'm not sure where that falls into
8 the labeling. Is that part of the discussion piece?

9 You know, we've spent really the majority of this time
10 talking about kind of the down side of using these things.
11 But, you know, a lot of times there's a down side of not using
12 these things, too. And I think if we're going to be looking at
13 the labeling as a whole, maybe this is a discussion point, but
14 I'm not sure how we wrap our heads around that.

15 And I've been kind of struggling. Several of the speakers
16 -- Dr. Namazy started it, and then Ms. Belsito really kind of
17 pounded it home with a lot of her anecdotes. And so will the
18 discussion piece -- I guess this is my question -- be a part of
19 that? Or can that be a part of that?

20 DR. YAO: Yes.

21 DR. BLALOCK: That was Dr. Yao saying yes.

22 DR. TRACY: Thank you.

23 DR. BLALOCK: Dr. Howlett.

24 DR. HOWLETT: Thank you. This is Elizabeth Howlett.

25 I'm also following up on Dr. Kreps's point that I think is

1 really important, and that is I think we have a situation of a
2 classic information overload, and we have a lot of information
3 that we want to try to present. And not only is the
4 presentation of that information very ambiguous, the
5 information itself is ambiguous.

6 And so the question I'm asking, and point of clarification
7 of, what kind of options are you open for to try to increase
8 the clarity of the ambiguous information? For example, just
9 came to mind, when I was working with the Institute of Medicine
10 on helping consumers interpret a sodium level, you know, they
11 had no idea, you know, is 1,000 mg good or bad?

12 And so we came up with a sort of a star system. So here's
13 the quality of the survey. This survey is a three-star survey.
14 This star is a four-star survey. So you could look at this and
15 see, well, you know, the strength of the evidence across -- so
16 are you open to other kinds of methods?

17 DR. NGUYEN: This is Christine Nguyen. The answer is yes.

18 DR. BLALOCK: Dr. Winterstein.

19 DR. WINTERSTEIN: I guess I still would like to clarify a
20 little bit what the question really is. There were a lot of
21 presentations and also a lot of questions about patient
22 counseling and how the information is getting to the patient,
23 and I wanted to review what information patients actually have.

24 There was a question whether they can get the label. Now,
25 the label is on a database called DailyMed that is maintained

1 by the National Library of Medicine, and if patients knew that,
2 then they would find them there. And if it's a brand drug that
3 they got prescribed, they would also find it likely on the
4 manufacturer's website.

5 But that's the only way they would find it, and many
6 patients probably wouldn't. So what they would have is
7 typically something that's called consumer medication
8 information, which is actually a mandate for pharmacies to
9 dispense. And this is the only time in the whole process that
10 a patient gets cared for that they get any written information
11 that is a pharmacy obligation to do.

12 We did a study more than 10 years ago that looked at the
13 quality of this information, and the amount of information that
14 is dispensed ranges from about 50 words to up to 5,000 words,
15 which tells us that the quality of that information might vary
16 quite a bit.

17 So this is the information that the patient would have
18 available unless there is a medication guide. And I think it's
19 very important to recognize that medication guides communicate
20 a very specific risk. And then the question of teratogenicity
21 of pregnancy, that would only be available if there were
22 already a confirmed risk about a pregnancy issue. Otherwise,
23 there is no medication guide that will talk about a pregnancy
24 problem.

25 So, basically, the label -- the leaflet or the package

1 insert that we are talking right now about is nothing that
2 patients have. And I would be extremely surprised if it were
3 used typically anywhere, in a pharmacy or in a physician's
4 office, to communicate any information to a patient.

5 So at the end of the day, I think it is essentially a
6 legal document, we know that, and perhaps a scientific document
7 that communicates information to prescribers. And if this is
8 the patient -- and if this is the question that we are trying
9 to answer here, you know, how can we make that communication
10 better, I think that's an important question.

11 But I think we should focus that question on exactly that
12 and not on something that has to do with communicating to
13 patients. And I just -- so this is my clarifying question: Is
14 this really the question that we're here to answer, because
15 then let's forget about the patient for a moment and really
16 talk about how do we structure the PI better so that physicians
17 get the information they need in order communicate that fact or
18 not. Does that make sense?

19 DR. BLALOCK: Yeah. Let me interject for just a minute
20 because I think, you know, Ms. Duckhorn is going to come up,
21 you know, after we take the break, and she'll be giving us the
22 charge. And I would think, as part of doing that charge, that
23 we'll have an opportunity to ask questions specifically about
24 the charge.

25 Is that true?

1 Okay. So I'm getting a nod. So thank you for the
2 question. And we'll pick it up when we're getting the charge.

3 Now, I've still got about five more folks on my list here.
4 And these should be questions for the speakers, including the
5 two FDA speakers. But let us do hold questions that relate
6 specifically to the charge until we come back after the break.

7 So Dr. Goldman.

8 Dr. Slovic?

9 DR. SLOVIC: I was just going to respond to a question
10 that -- it came up with regard to something that Dr. Kreps
11 said, but it was a while back, and I think it's not really --

12 DR. BLALOCK: Okay. Maybe again, responding to the
13 comments made by other Committee members, that's really best
14 left for the discussion.

15 DR. SLOVIC: Yeah.

16 DR. BLALOCK: So this is truly questions for the speakers.
17 You can tell I need fresh soda.

18 (Laughter.)

19 DR. SLOVIC: Well, let me just phrase it with regard to
20 the very interesting survey that Dr. Namazy presented this
21 morning. And then a question came up, and there seemed to be
22 an inconsistency between the question, which asked, did you use
23 this labeling information; 73% said yes. But they seemed to
24 prefer the letters. So if they used it, why do they prefer the
25 letters?

1 Well, I think I've had some experience with this question
2 about what's it mean when you ask someone if you used
3 information. We don't necessarily know what, how we're -- if
4 or how we're using information. My sense was probably the
5 answer that you got there was based on the fact that people may
6 have looked at the information at some time, you know, a little
7 bit, they glanced at it, they saw something in it that was
8 interesting.

9 That doesn't mean -- you know, that's the tip of the
10 iceberg with regard to using the information. I think the only
11 way to know how adequate the use of the information is, is to
12 test it, you know, to run these things by people and listen to
13 them as they think out loud about how they are taking in that
14 information and doing something with it.

15 And then you'll find out the extent to which people are
16 using it, whether different people use it in different ways or
17 adequate or inadequate ways. Just looking at a piece of
18 information doesn't mean that you're using it.

19 DR. NAMAZY: I completely agree. I mean, I think that
20 that was a little bit vague, that first question. Sure. I
21 mean, they may have looked at the PI at some point. But I
22 think what kind of came down to it, though, in the survey is
23 that a lot of the clinicians still revert to the pregnancy
24 categories, and when faced with the sample narrative, they
25 still would have a hard time navigating to it and go back to

1 the letter category system.

2 DR. BLALOCK: Thank you. Two more questions before the
3 break.

4 Dr. Cappella.

5 DR. CAPPELLA: I didn't have any clarifications. I only
6 had suggestions, so I withdraw.

7 DR. BLALOCK: Okay. And Dr. Lyerly.

8 DR. LYERLY: So I have a question for the FDA, and I think
9 it arose during Dr. Sahin's talk, when she was going through
10 the labeling, the example labels, and was talking about the
11 fact, I think, that there -- these were examples of labels that
12 did not show a major teratogenic effect.

13 And I guess what my question is, is whether you could
14 offer a little bit more information about how you think about
15 what that threshold for a major teratogenic effect is, and then
16 how you think about the role of reporting data that suggests a
17 teratogenic effect in one direction or not and putting it up
18 against a statement that it basically doesn't meet the
19 threshold for clinical relevance in some way.

20 So I guess I would just like to hear more about how you
21 think about that space of not yet teratogenic effect, and when
22 is it that you get there and communicate that.

23 DR. YAO: We can provide -- I think I heard that there
24 were maybe two things we could provide examples for after the
25 break. The first was -- and I forgot already. A medication

1 guide, right. We can provide an example of Section 17, which
2 is patient counseling information and medication guide.

3 The second thing I think we could help with, at least to
4 give some -- I don't think it'll answer your question all
5 completely, Dr. Lyerly, but an example of when we are convinced
6 there is a teratogenic effect, how do we describe that? And
7 how does that differ potentially from what, the other examples
8 we've provided?

9 And I might also say that the labeling as a clear
10 teratogen with warnings and precautions, maybe even a REMS on
11 occasion, actually may not even necessarily be based on what we
12 know to be, you know, be derived from human data. It may be
13 from something earlier, and a clear effect, you know, in animal
14 toxicology studies that would lead us to that. So we can
15 definitely provide a couple there, if that would help the
16 Committee.

17 DR. BLALOCK: Okay. And I think that brings us to the end
18 of the questions, so let's go ahead and take the break. And
19 I'm looking at my watch. It looks like a -- let's resume at
20 3:50. And I'd just remind the Committee members again not to
21 speak about the topics that we're discussing during the break.
22 So we'll resume at 3:50.

23 (Off the record at 3:31 p.m.)

24 (On the record at 3:50 p.m.)

25 DR. BLALOCK: I'd like to call the meeting back to order.

1 (Pause.)

2 DR. BLALOCK: And, Ms. Duckhorn, would you like to review
3 the charge to the Committee now?

4 MS. DUCKHORN: The moment you've all been waiting for?

5 Thank you, Dr. Blalock, members of the Committee, and
6 guest speakers. We've heard a lot of interesting presentations
7 framing the issue, and you've asked a lot of great questions.
8 This meeting is to obtain your advice on how information
9 in labeling under the Pregnancy and Lactation Rule is being
10 perceived and used by healthcare providers and other
11 stakeholders, factors that are critical to healthcare
12 providers' interpretation of the data and counseling of
13 pregnant women on the risks and benefits of medication, and how
14 to convey risk information to healthcare providers to
15 accurately and adequately inform risk-benefit considerations
16 for medication use during pregnancy.

17 We ask that you respond to a series of discussion
18 questions located in your packets and as separate handouts.
19 For your convenience, we will project the questions as you move
20 through them.

21 Question 1. First, discuss how the factors below impact
22 healthcare provider decision making and patient counseling, in
23 terms of risk perception, interpretation of uncertainties and
24 available data on drug use in pregnant women, context of
25 drug-associated risks in relation to the background risk

1 information on major birth defects and miscarriage, benefit-
2 risk considerations, and medicolegal considerations.

3 Do you want me to read all of them, or just go --

4 DR. BLALOCK: So open it up for discussion.

5 MS. DUCKHORN: Sure. Or do you want me to read all four?

6 DR. BLALOCK: I'm sorry.

7 MS. DUCKHORN: Let's move to the second question. I'll
8 just --

9 DR. BLALOCK: Okay.

10 MS. DUCKHORN: -- go through them. Okay.

11 2. Discuss how effective PLLR has been in conveying
12 safety evidence in pregnancy that is useful to benefit-risk
13 decision making. Include in your discussion the following:

- 14 - Interpretability of safety evidence in drug
15 labeling;
- 16 - Interpretability and impact of animal data on
17 decision making when there are no human data;
- 18 - Information that has been unhelpful or has led to
19 unintended adverse consequences (for example,
20 avoidance of needed treatment).

21 And if appropriate, recommend strategies to improve risk
22 communication that comply with PLLR requirements.

23 2B. Consider the following situations and discuss best
24 practices to communicate the following in drug product
25 labeling, if appropriate:

- 1 - Observational study data where inconsistent study
- 2 findings preclude a clear conclusion;
- 3 - Observational study data where the weight of
- 4 evidence show no increased risk for major
- 5 malformations, but some data suggest an increased
- 6 risk;
- 7 - Observational study data where there are
- 8 methodologic limitations (for example, when to
- 9 include or not to include these data);
- 10 - When there are no study data, but cases reported in
- 11 the pharmacovigilance safety database are available.

12 3A. Discuss your interpretation of the following phrases
13 currently used in the PLLR Risk Summary, and provide any
14 suggestions for improvement, if applicable: "adverse
15 developmental outcome," "limited data", "available data are not
16 sufficient to inform the risk," "available data have not
17 reported a clear association."

18 3B. Discuss how language affects the following:

- 19 - Physician willingness to treat pregnant patients;
- 20 - Patient decision making and adherence to treatment;
- 21 - Pregnancy planning and prevention (for example,
- 22 need for pregnancy testing before prescribing a
- 23 medicine).

24 3C. Discuss intended and unintended consequences,
25 including prescriber liability, that may occur with certain

1 language or communication approaches.

2 4A. Suppose FDA has some evidence of a potential drug
3 safety issue for pregnant women, but the evidence is limited
4 and preliminary. What should FDA consider in deciding when and
5 how much to communicate to the public about what it does and
6 doesn't know? And what should FDA consider in deciding whether
7 to wait?

8 4B. Suppose FDA has determined that communication about
9 the potential for adverse effects in pregnancy is necessary.
10 What additional comments do you have about how FDA can
11 communicate to maintain a balanced assessment of the benefit
12 and risk and to minimize unintended adverse consequences?

13 DR. BLALOCK: Okay. So now you wanted to open it up for
14 discussion. Or there was some talk before the break of
15 providing a medication guide. Was there a decision on that?
16 And I think something else as well.

17 DR. YAO: We're happy to do that if the Committee would
18 like to see some examples. We're ready to provide those. So I
19 have my colleague, Dr. Tamara Johnson over there, working with
20 our audiovisual expert.

21 So the first thing we were going to present was the
22 Section 17, patient counseling information. As we're
23 projecting, I do want to make sure it's very clear to the
24 Committee that all we did, for purposes of just clarifying and
25 providing examples, pull up something that we knew was an

1 example. This is not intended to be singling out this product
2 in any way. And so I want to make sure that the Committee is
3 very clear about that.

4 So this is Thalomid, which we thought would be a fairly
5 straightforward example of a product, a thalidomide, where you
6 can see this is the information that we generally include in
7 Section 17, patient counseling information. And you can --
8 sorry, patient counseling information is here.

9 So as we had described, patient counseling information is
10 the last section in standard prescription product labeling, and
11 it's intended to give a prescriber or someone who's having a
12 conversation with the patient some important information about
13 serious warnings and precautions, and also to counsel about any
14 programs that would be available that are needed to gain access
15 to the product. And in this case, Thalomid is only available
16 through a REMS program, and that's Risk Evaluation and -- REMS
17 is Risk Evaluation and Mitigation Strategy, right.

18 So this is the patient counseling information. And then
19 if we scroll down, I think we have the beginning -- yeah, we
20 close out the -- this is the medication guide. So this is
21 written in language that is again, bulleted, single concepts,
22 and in language that is intended for the patient.

23 Are there any questions or comments about this?

24 DR. BLALOCK: Dr. Lee has a question.

25 DR. YAO: Sorry.

1 DR. BLALOCK: Dr. Howlett. And your microphone.

2 DR. HOWLETT: Okay. Point of clarification: What percent
3 of the drugs that you're dealing with are this clear cut? It
4 seemed like, you know, all the examples that we were looking at
5 was like, oh, maybe this, maybe that, who knows. And this is
6 like, you know, this is clear.

7 DR. YAO: So you -- if I could respond. This is Lynne
8 Yao.

9 So we didn't present these in your briefing document
10 because we kind of do feel like we know how to label something
11 when we have clear information. This was really to provide you
12 a little bit of additional context to, you know, show you when
13 we know something and how we describe it versus when we're less
14 sure. And I would say that the universe of products like this
15 is extremely small.

16 DR. BLALOCK: Dr. Lee.

17 DR. LEE: Okay. So I'm thinking back to Dr. Kreps's
18 question and Dr. Wolf's question from before about the
19 uncertainty of the data and the response you just gave.

20 So I think of medicines as like four buckets. The first
21 is it's safe for the pregnant woman; it's unsafe for the
22 pregnant woman; risk is known and that's balanced with other
23 factors; and then there's risk is unknown.

24 So of the percentage that you describe, I'm expecting that
25 Questions 2 and 3 relate to bucket 4. Is that correct? Is

1 that what you're asking us, to message things that have unknown
2 risk or uncertainty?

3 DR. YAO: Generally speaking, yes. When the data are
4 limited or there is conflicting information or that we don't
5 have a clear --

6 DR. LEE: And what percentage of medications fall into
7 that category?

8 DR. YAO: The majority.

9 DR. NGUYEN: So -- yeah.

10 DR. YAO: The large majority.

11 DR. NGUYEN: I would clarify that something this clear,
12 thank goodness, is pretty uncommon, when the risk is
13 undeniable. Conversely, it's also rare for us to say that the
14 drug is perfectly safe in pregnancy. And where you see that,
15 really, are more of the products that are approved to treat a
16 pregnancy-related condition because the safety data have been
17 adequately generated for those specific products.

18 For the most other products, which is the vast majority,
19 is going to be in the nebulous two buckets that you described.

20 DR. LEE: Yeah. And I think that's one of the challenges
21 that prescribers have is that your uncertainty is coming down
22 to the prescriber, and we don't know what to do. And I think
23 that's the challenge that we're seeing based on what you guys
24 are trying to convey.

25 DR. NGUYEN: We completely agree. I mean, I think it's a

1 two-phase situation. One, we have to label the information
2 that we have now, and we know that information is far from
3 perfect so we're discussing how best to do it, how best to do
4 in the way that's the least confusing and hopefully useable.
5 And then certainly we -- at a federal level, we have
6 discussions of how can we stimulate research in pregnant women
7 so we actually can get the information that's needed.

8 DR. BLALOCK: Let me ask you all just one question.
9 You're going to -- you know, you came back and showed us the
10 medication guide. Was there another document that you wanted
11 to show us as well?

12 DR. YAO: Sure. The last one is --

13 DR. BLALOCK: Let's look at that before I take more
14 questions.

15 DR. YAO: Okay. The last one is an example of PLLR
16 product labeling in which we have a clear risk based on human
17 data. I did include that sometimes we'll label it based on
18 animal data too, but in this particular circumstance -- again,
19 as just an example. We are not here to discuss this particular
20 product in any way.

21 But as an example of how we have communicated the
22 information when we have human data that describe a clear risk
23 during pregnancy, the example is here. So this is Section 8.1,
24 which actually describes a pregnancy registry too, but the risk
25 summary is what I would direct you to.

1 There's also information as it refers you back to --
2 actually you're not supposed to refer back up, but it talks
3 about clinical considerations. And if you go up to warnings
4 and precautions and the boxed warning, it's all in there.

5 So can we scroll up to boxed warning as well?

6 So there's the box, embryo/fetal toxicity. And then it's
7 also described in a little bit more detail in warnings and
8 precautions, Section 5.3. And we can go there, and that's
9 where it's listed, in terms of the risk that we've identified,
10 in terms of human clinical data, and then again in the risk
11 summary, and then the human data sections of 8.1.

12 DR. BLALOCK: And let me just clarify. This is the
13 professional package insert?

14 DR. YAO: Yes.

15 DR. BLALOCK: Okay.

16 DR. YAO: This is -- and this is an example, just an
17 example of PLLR converted labeling that includes -- again, when
18 we've been clear, we've felt like we were clear that we knew
19 that there was a clear risk, based on human data, this is how
20 it has appeared.

21 DR. BLALOCK: And, you know, and in the materials that we
22 were sent prior to the meeting, I think that there were
23 actually, at the back of those, eight different examples of
24 this.

25 So Dr. Wolf.

1 DR. WOLF: I mean, I guess just a couple of comments
2 because I think I'm getting my -- I've totally understood my
3 issue now with the counseling piece, that it still comes back
4 to what do you want to accomplish in terms of the outcome? And
5 I get it, getting rid of the ambiguity and the uncertainty,
6 which we deal with a lot, in terms of how do you communicate
7 uncertainty to the patient, but you're actually saying that
8 this may stop short because it may never get to the patient.

9 But the odd thing here is the default seems to be, from
10 the data this morning, is that people, that prescribers are not
11 using products when they could be potentially used but it's
12 still kind of unknown. So this is -- I mean, I'm a little bit
13 kind of now in the ditch with you and understanding the full
14 appreciation of the problem.

15 I guess one comment would be also is do we know the
16 difference between -- you know, there's all this information
17 coming out, especially with new medications, where there may be
18 more unknowns where especially a lot of these products,
19 especially when we were talking about SSRIs earlier, may be
20 more commonly used in primary care, which is the work that I
21 mostly focus in on, where there is more reticence to not want
22 to -- you know, the default, well, if there's any issue, even
23 if it's ambiguity, I'm just not going to do it.

24 Has that been something that's kind of been clarified? I
25 mean, it doesn't change how you message it, other than the fact

1 that this is a lot of content that will definitely not -- I
2 mean, they'll stop short of the black box in terms of trying to
3 figure out whether or not they're going to learn more about how
4 they might potentially use it.

5 DR. YAO: Lynne. Yeah, so let me just clarify again.

6 Our goal is, as you've read -- heard the questions and
7 we've provided just a couple of examples to sort of say this
8 when we've been more certain. The examples that Dr. Sahin
9 presented earlier are examples when we've been less certain.

10 We need help in understanding whether the statements that
11 we have used, and that's part of the first couple of questions,
12 does that -- are those statements helpful? How are they not
13 helpful? How do they -- do they persuade you? If you are
14 unlikely to prescribe, to not prescribe, are you swayed to
15 prescribe if you were not going to -- again, we want some
16 information and feedback from you about how these statements
17 may be helpful or unhelpful.

18 DR. WOLF: And if I could just follow -- because I think
19 this is really helpful so we don't spend not only the rest of
20 today but tomorrow providing you feedback on things that you
21 already know, and as the titan -- this is a very narrow ask.
22 Am I interpreting it correct, in terms of what you want the
23 RCAC and other members today talking about?

24 It's really about the messaging and only the messaging
25 specific to the prescriber and not a lot of the ancillary

1 stuff. You don't want us talking about more data and all these
2 other issues. You want us at the ground, okay.

3 DR. BLALOCK: Dr. Nahum.

4 DR. NAHUM: Yes. Thank you. Dr. Nahum.

5 You know, just listening today, I just want to -- I have
6 two questions for FDA. But it sounds like this is not so much
7 a communication deficit, per se, as it is a knowledge deficit.
8 It's very difficult to communicate well when you don't know
9 what it is you're trying to communicate.

10 And so I think that's part of what is going on in terms of
11 some of these questions. Dr. Lyerly asked a question before as
12 have several others that I did not really hear an answer to.
13 And this revolves around the question, really, of what a
14 minimally clinically important difference should be considered
15 with regard to risk for teratogenicity.

16 I know that FDA had previously set a threshold with
17 registries, for instance, of a relative risk or an odds ratio
18 of 2, 2.0. And this was there for a while. It got kind of
19 rolled back. But that, at least, would put a stake in the
20 sand, if you could give us a number like that.

21 And what this gets back to, really, is the idea of
22 powering. And when we run clinical trials, you know, for
23 primary approvals, to demonstrate safety and efficacy, we
24 always have to power these trials. And we're not sure what the
25 result is until we get either to the end of the trial or a

1 certain number of events or something like that.

2 That's not what you're telling us here. That's not what
3 I'm hearing. There's sort of an undercurrent here of a rolling
4 assessment of incoming data, as it comes in, and that we should
5 update information in labeling and communications based on
6 that, even if the difference is not clinically important, or if
7 it's not statistically significant in a robust sense.

8 So I guess what I'm asking you here is can you give us
9 some guidance as to what you would consider to be a clinically
10 relevant change in the acquisition of new information and its
11 processing, so we know when to communicate things, what to
12 communicate, and when to update labeling?

13 DR. YAO: Lynne Yao.

14 So I think that's a very fair question. And I think it's
15 a very fair point, but that's not the point of this Advisory
16 Committee, I'm sorry to say.

17 We really -- and you're right, we've published in guidance
18 that says, you know, we want to power a prospectively --
19 prospective pregnancy registry to identify a relative risk of 2
20 or greater, and you may look at the labelings and the pregnancy
21 registries we have open on our FDA website and know that these
22 registries have been running for years and years and years.

23 So that's a whole separate issue about what data qualifies
24 as sufficient to change labeling. And that's a conversation
25 that we have with given, you know, companies on a daily basis.

1 But when we've decided that there's information that should be
2 included in labeling, are we communicating in that way that
3 describes the uncertainties, the information that we have?
4 That's really at the heart of what we'd like to have the
5 Committee describe or give us advice on, partly because we're
6 500 labelings into this, and we don't know if we're doing what
7 we have been told we should be doing under the intent and
8 spirit of the rule, of the PLLR.

9 DR. NGUYEN: And --

10 DR. YAO: I would be -- sorry. I just would be interested
11 to make sure I am accurately reflecting others' position at
12 FDA.

13 DR. NGUYEN: Yes. So I would just add the clarification
14 that we're in a position now that we have to put available data
15 in labeling. It's the good, bad, and ugly. We're not tasked
16 with only putting in information that's going to change
17 practice. It may do that, but the vast majority of the time,
18 we have to put in what we have, and we're trying to do it in
19 the way that hopefully best serves the public, and so that's
20 where we need feedback from you.

21 DR. BLALOCK: Dr. Spong, it seems like you want to react
22 to something that was said.

23 DR. SPONG: Right. So this is Cathy Spong. And I think I
24 just want to provide, if I may, since we're in the discussion
25 period, for the Panel members who don't deal with this on a

1 daily basis, that in pregnancy, we don't have the randomized
2 trials on the majority of medications that people are taking.

3 These medications are put through randomized trials, but
4 they are not in general inclusive of pregnant women. And
5 oftentimes when a woman becomes pregnant, she is then removed
6 from the trial, and we do not get that outcome information from
7 that patient.

8 So yet, if you can believe it, there's a lot of women who
9 get pregnant in this country and around the world, and many of
10 those women are taking medications, and they continue to take
11 those medications when they are lactating. And yet that
12 developing fetus and that developing neonate and all of the
13 exposures that they can have, we don't have information to
14 provide those women and their families on how best to give
15 those medications.

16 I think it's important to understand, and I really
17 appreciate the clear presentation this morning, that
18 medications that are approved for use in adults, it's not that
19 they are off label in pregnancy. They're still approved. If
20 that -- if the reason that they're on that medication is still
21 happening in pregnancy, right, so they still have asthma or
22 they still have hypertension, they're on-label use of that
23 medication. Yet how do we counsel that woman about what the
24 impact is for the fetus and for the neonate?

25 If we think there's a dearth of information in obstetrics,

1 and there is, there's even more of a dearth of information in
2 lactation. Yet we have to provide that information. And we,
3 as providers, have to counsel these women and their families.

4 And I think what we're being asked today is to say, is
5 this PLLR, in its new revised state, providing the information
6 that you want to be able to get across to these people? Yeah,
7 the data's not good. We're not going to change that today.
8 We're trying to change it; we're trying to do what we can. But
9 how do we get the information across given that we have to put
10 it in there? So if there is some animal data, we've got to put
11 it in there. How do we make it understandable that it is or is
12 not translatable to humans?

13 And I think, just going back to Dr. Lee's question
14 earlier, you know, is it safe, is it efficacious? We don't
15 know about that in pregnancy, to be perfectly honest. And what
16 is safety? Right. Is safety not a malformation? Is safety
17 not ADHD? Is safety not being retained in kindergarten? Is
18 safety not going to a public university? I don't know what
19 safety is. But it's really difficult in pregnancy to ever say
20 something is truly safe.

21 DR. BLALOCK: I've got five more questions here, and then,
22 you know, when I got through these, then I really do want to
23 get to the questions and start us to focus the discussion of
24 the questions that the FDA wanted to have answered.

25 So let me just say, the folks I've got are Goldman, Baur,

1 Tracy, Slovic, and Pleasant.

2 So Dr. Goldman.

3 DR. GOLDMAN: Could -- this is Myla Goldman.

4 I guess -- I have a question depending on your answer to
5 this, but to clarify, the counseling piece, which is different
6 from the patient information, the physician counseling piece,
7 is that encompassed in what we're looking at? Is that
8 considered part of the package insert?

9 And is pregnancy always a component of the counseling
10 piece, or is it only present or absent depending on what's
11 known about that particular agent? Could you clarify that?

12 DR. YAO: So it is under discussion, but in the -- as I
13 think Dr. Wolf has articulated, and Dr. Spong, thank you both
14 for, you know, speaking very clearly what I don't think I was
15 able to do. But in those situations in which there is really
16 uncertainty and different levels of uncertainty, we still have
17 to, and we're required by the rule to, provide that
18 information, communicate that information.

19 That's less likely -- in those situations, it's less
20 likely we're going to have something in patient counseling.

21 DR. GOLDMAN: So I think --

22 DR. YAO: So it's -- so --

23 DR. GOLDMAN: Yeah. So then I have a comment, I guess.
24 Is this -- okay. So it seems to me, in summary, sort of from
25 the day, that there is sort of two -- I mean, there's really

1 three end-users, but two end-users. One is the provider, who
2 is trying to make the best decision at that moment about that
3 individual patient, but then sort of the second, secondary
4 end-user that has been identified are these women who are
5 living with chronic disease, who are making forced decisions
6 between their illness and potentially the health of their baby.

7 And so to me, if it's not part of the PLLR, it seems
8 obligatory to protect against that second end-user, that the
9 patient counseling segment needs to always be inclusive, and
10 particularly when information is not known, to emphasize on the
11 risk of the disease itself.

12 And this gets back to a point that I think was made by our
13 patient representative advocate about that we can't separate
14 these two. And I understand the language, right, that so we
15 can't have patient language in the physician insert, but we
16 could use the physician counseling segment as a way to protect
17 that second end-user, which is protect women living with
18 chronic disease from these forced choices off of drug, when we
19 know that the disease itself is devastating to them, as in the
20 case that I sort of navigate every day.

21 DR. NGUYEN: Hi. Christine Nguyen.

22 So I think I just want to tease apart Section 17, called
23 patient counseling, from the general concept of patient
24 counseling.

25 DR. YAO: There's specific language, right?

1 DR. NGUYEN: There's specific criteria. And as Dr. Yao
2 mentioned before, usually the elements that would drive a
3 certain piece of information to go into patient counseling has
4 to do with warnings, precautions, pregnancy testing, or any
5 other specific testing before you're supposed to take the drug,
6 adjustment in dose, those type of information.

7 As far as what you're describing, in terms of pulling out
8 and translating the available data in pregnancy and then
9 counseling that with the risk of an untreated illness, that
10 information is contained in Section 8. And so that's why we
11 keep going back to this section.

12 If we have information on pregnancy that does not provide
13 a clear risk in pregnancy, it's the elusive language that you
14 saw this morning, that will not be pulled into Section 17, the
15 patient counseling. Again, as I mentioned, the purpose of
16 Section 17 counseling is very specific to those elements that I
17 described, adjustment in dose, special warnings, precautions.

18 So, I mean, part of that has to be -- it's a little bit of
19 FDA educating the public, what information lays where in
20 labeling and how to use it.

21 DR. GOLDMAN: I guess I --

22 DR. BLALOCK: I think we --

23 DR. GOLDMAN: Yeah, okay. Perfect.

24 DR. BLALOCK: -- keep moving.

25 Dr. Baur.

1 DR. BAUR: So Cynthia Baur.

2 So, Dr. Blalock, I have just a procedural question for
3 you. Given that we have these three blocks of discussion, and
4 I'm sure that all of us have lots of advice that we want to
5 offer, will we be -- will the discussion be structured around
6 those four questions then, or how do you envision that?

7 DR. BLALOCK: Absolutely. And, in fact, you know, I'm
8 probably trying to push people a little bit to end this
9 discussion right now so that we can get to the questions which
10 the FDA has prepared and would like to have us respond to.

11 So what we'll go do is go through each question
12 individually.

13 DR. BAUR: Okay.

14 DR. BLALOCK: And I do intend to end pretty promptly at 5.

15 DR. BAUR: Okay.

16 DR. BLALOCK: You know, even if it's in mid-sentence.

17 (Laughter.)

18 DR. BAUR: So I do have a question for the FDA but not
19 about the things people have been talking about.

20 DR. BLALOCK: Okay.

21 DR. BAUR: I wondered if the FDA staff had decided if,
22 because this is public information, if the federal Plain
23 Writing Act applies to this, because if it does, then that
24 provides certain guidance already in terms of the way that you
25 would approach providing this information to clinicians. So

1 has anyone done that determination yet?

2 MS. DUCKHORN: Hi, Cynthia. As you know, plain writing
3 means it's written for its intended audience. In this case, I
4 mean, the labels are written for the intended audience of
5 prescribers. But these labels do not go through any kind of
6 testing, or they don't use the Clear Communication Index, for
7 example.

8 DR. BAUR: Right. No, I was thinking more some of the
9 techniques around, you know, the way information is organized,
10 making sure that you have a main message, those kinds of
11 things, even if you don't -- so just in full disclosure, I have
12 a tool, when I was at CDC, called the Clear Communication
13 Index, and that's what Jodi's referencing.

14 But also, just in terms of the Federal Plain Language
15 Guidelines, that's a set of guidelines that all federal
16 agencies are supposed to use when providing public information.
17 So there's kind of a foundational set of principles that might
18 guide that. So I just wondered if that determination had been
19 made. That would provide some direction already in terms of
20 kind of simplifying and structuring some of this information.

21 DR. BLALOCK: Thank you.

22 Dr. Tracy.

23 DR. TRACY: I actually have a question about the
24 questions, so I'll wait.

25 DR. BLALOCK: Dr. Slovic.

1 DR. SLOVIC: Right. So we have the science that underlies
2 the development of medicines. It's very elaborate, expensive;
3 it takes a lot of time and effort and money. And sometimes
4 it's not definitive, particularly in this case with pregnancy,
5 where sometimes you can't do the studies that you would like to
6 be able to do to get better data.

7 So you have all of that, and this provides information, as
8 I understand it here, that is going to go to providers. And
9 the question, since this is a meeting on communication, is, you
10 know, how adequate is this information? How, you know, how
11 could it be improved?

12 There's a lot of questions that have been put forth. And
13 I don't know that we know the answers to those questions. Now,
14 we can sit around the table, and we can all speculate on those
15 questions. But there's another way to answer those questions,
16 and it's a lot easier than the science of developing the
17 information to design the drugs and so forth.

18 It's the science of risk communication. The fundamental
19 tenet is test your messages. It's very easy; it is far easier
20 to take various communications and then try them out on
21 representatives of your audience and see how they react to
22 that. Ask them questions, get their, you know, open-ended --
23 you can do this. It's very, very easy, and you always learn.

24 What you learn in the area of risk is that risk is
25 complex, that people respond and interpret it in ways that you

1 might not have expected them to do it, even professionals. We
2 use -- risk is very difficult to understand, and so we have all
3 kinds of mechanisms to try to simplify it. I mean, that's why
4 we go to the ABC kind of thing is because, you know, it's a way
5 of simplification, something that's complex.

6 So is it within FDA's purview to do research or to sponsor
7 research to try to answer some of the questions you're asking
8 of us?

9 MS. DUCKHORN: They may not like this answer. This is
10 Jodi Duckhorn.

11 We do have the ability to do testing, to do cognitive
12 testing. And unfortunately for -- most of the time, the time
13 that it takes to do testing is not built into the timelines
14 that are allowed under the user fee authorizations. And so
15 they're already in very tight timelines, and there's just not a
16 lot of time built in for testing.

17 If after the fact, after a drug is approved or on the
18 market and the label is out there, if one of the reviewing
19 divisions came to my staff and asked us to do cognitive
20 testing, we could do that. And it just opens a new timeline
21 for a lot of back and forth with the sponsor and the division.

22 DR. SLOVIC: So let me just speculate. My guess is that
23 if you were to do testing on things other than something like
24 thalidomide, where you've got these inconsistent results or
25 lack of human data, animal data that is complex and

1 inconsistent, you'd find that the communication is a mess, that
2 it wouldn't be effective. People would interpret the
3 message very differently from one person to the next. They
4 wouldn't find it helpful for decision making. That's just a
5 speculation, but it could be tested.

6 DR. BLALOCK: And I think, Dr. Slovic, that, you know, a
7 lot of people in this room would, you know, would agree. And,
8 you know, I think that some of the questions that we'll be
9 addressing really will, you know, sort of invite that as a
10 recommendation. So I think that that will come -- you know,
11 the user testing as a recommendation from this meeting. I'll
12 be surprised if it does not.

13 But let me -- Dr. Pleasant has a question. Oh, he's
14 passing. I'm going to, so call this portion to an end then.
15 And if I can get pulled up the first question.

16 So there are four questions that our charge is to discuss.
17 And part of my job up here is, towards the end when we get done
18 discussing, is to try to summarize. And so, you know, I know
19 that it's hard to, you know, sort of stay focused on the
20 questions, but as much as we can do that and compartmentalize
21 and really focus on the questions makes my job easier.

22 And do we -- are we going to get -- there's the first
23 question. So I'm going to -- actually, Dr. Cappella had a hand
24 up earlier.

25 So the first question, discuss how the factors below

1 impact healthcare provider decision making and patient
2 counseling. And you can read the factors here yourself.

3 Dr. Cappella, did you have a comment in response to that
4 question?

5 DR. CAPPELLA: I can find a way of turning my comment into
6 an answer to this question.

7 DR. BLALOCK: Oh, since I kind of put you on the spot,
8 I'll let you.

9 DR. CAPPELLA: That's okay. No. I would focus on
10 Subpoint B here. There is -- and this is in, partially in
11 response to Paul's observations as well, and that is that we --
12 while we don't have data about presenting information --
13 informational uncertainty with regard to the particular drugs
14 we're talking about in pregnant women, we do have a lot of
15 evidence that suggests that in the press, broadly, when there
16 is conflicting information about diet, about behavioral actions
17 that are healthy versus unhealthy, the role of red wine, white
18 wine, whole grains, not whole grains, and so on and so on, when
19 there is controversy within the public information environment,
20 part of what we know is that this increases people's
21 uncertainty and frustration and cynicism about those particular
22 products and also about the science behind them.

23 And so part of what I think is of great concern here, and
24 I think this is part of what Paul is referring to, is the
25 notion that the presentation of information in terms of the

1 degree of uncertainty that is available from the prevailing
2 science will undermine the way in which people view that
3 science and probably undermine, to some extent, the credibility
4 of the communication about that science.

5 That concerns me a great deal. And I think that, you
6 know, how that is communicated and the way in which that can be
7 framed so that it somehow mitigates the cynical response that
8 might result is a real challenge. And I don't have any ready
9 answers to that, but I think that that -- I take that to be the
10 challenge that you're putting before us.

11 DR. BLALOCK: And, Dr. Slovic, since you were referenced
12 in that comment, let me turn the microphone to you for a
13 minute.

14 DR. SLOVIC: Well, I agree with that comment, but I wanted
15 to address the risk perception, first point there, or more
16 broadly the concept of risk, which we use all the time, and
17 refer you to Elizabeth Conover's very excellent presentation
18 this morning of all of these factors that influence how we
19 judge probability.

20 But I think 90% of her talk addressed risk as a
21 probability. And she even said, well, maybe it's better to use
22 chances rather than risk. And I think one of the problems in
23 thinking about communicating about risk is that risk has
24 multiple definitions, of which probability is one.

25 So there's at least -- there's more than four, but the

1 four that are, in my mind, most prominent and illustrate the
2 problem of communication, the first is risk, we use risk when
3 we mean a hazard. Something's dangerous. You know, like
4 airplanes are a risk. It's a hazardous thing.

5 A second definition is risk as a probability, you know,
6 what's the risk of some consequence. We're implying what's the
7 probability?

8 A third definition is risk as a consequence. So what is
9 the risk of getting, of letting your parking meter expire? The
10 answer is getting a ticket. That's a consequence.

11 And the fourth definition, I think, is perhaps the most
12 defensible, if you want to talk about risk, which is, risk is
13 some combination of the likelihood of something going bad and
14 the severity of the consequences. What's the risk of riding a
15 motorcycle? What's the likelihood of different kinds of
16 accidents and the severity?

17 And I think if we talk about risk and we really mean
18 probability, we should say probability, and it's very -- you
19 know, there's a lot known about how to communicate
20 probabilities.

21 And the problem -- but one of the problems with using
22 probability as your definition of risk is it leaves out the
23 severity of the consequences. So a well-known risk perception
24 researcher did a study of a whole bunch of different
25 consequences and asked for the judgments of risk.

1 And some of these were pretty serious, but what came to
2 the top, the item that was judged riskiest of all these things
3 was getting the wrong change in the grocery store because it
4 was more likely than some of the other things, like getting
5 AIDS. Okay, getting AIDS is less likely, so people judge it as
6 risky.

7 So we have to also consider consequences in risk. So
8 that's just the beginning of thinking about communication. And
9 it gets more complicated from there, but I'll stop here.

10 DR. BLALOCK: Let me ask you a follow-up question, though.
11 You know, in the context of healthcare provider decision making
12 and patient counseling, you know, how would you make that link?
13 What are the implications, do you think, of what you, you know,
14 just were describing in relation to healthcare provider
15 decision making and patient counseling? Do you use certain
16 words rather than others?

17 DR. SLOVIC: Again --

18 DR. BLALOCK: Just as an example.

19 DR. SLOVIC: Again, I think you have to test your
20 messages. The problem is that even -- we talked about having
21 clear information. Even if you have clear information about
22 probabilities, then you have the question, well, how do you
23 express the probabilities with some -- Conover presentation.
24 Or in the book that you referred to that Baruch Fischhoff
25 edited, I'm sure it's in there.

1 So, for example, if something -- if you say -- even if you
2 have good data and you say, well, if you take this drug, you
3 have a -- 1 in 100 pregnant women will get this certain
4 consequence. Okay. That's 1% or it's a 0.01 probability or
5 it's 1 in 100.

6 Each of those framings will lead to a different response.
7 If I want that person to be more concerned, I'll say 1 in 100,
8 because we know that that -- people image the numerator. They
9 think -- they have an -- they think, well, maybe I could be the
10 one. And that scares them. And that feeling then becomes a
11 representation of risk.

12 If you said that the probability is 1%, that's a small
13 number. It doesn't create that image. So then, so which way
14 should you present it? Both ways, one way? And that's where
15 we have clear data.

16 DR. BLALOCK: Dr. Spong.

17 DR. SPONG: Thanks. I think that, you know, going
18 specifically to this question, all of these clearly impact how
19 providers, and I'll call myself a provider for this question,
20 give that decision making and that counseling. And I think,
21 going back to this question of 1 in 100 or 1%, or you could say
22 99 out of 100 will not, right.

23 And oftentimes when I'm talking to a patient, I'll say,
24 you know, your risk is this, whatever 1 in whatever it is, and
25 I'll say, you know, I've got patients where it's 1 in 5 versus

1 1 in 10,000, and they may make very different decisions because
2 it's based on what your perception of that risk is.

3 And I think it was really important, as was brought up
4 earlier this morning, that patients and people need to realize
5 that they're taking risks every day. And just because they're
6 making a risk decision on this medication, they're making --
7 and yet they were willing to get on the D.C. highways and come
8 and see me in my office and not even think about the potential
9 risk that they were having there, right.

10 So it's risk out of context. Everything we do involves
11 risk. And so to have that communication with the patients to
12 explain to them, this is just one of many, many different
13 things.

14 But the risk itself isn't the only thing. You know, if we
15 don't have for them to tell them whether or not the studies are
16 strong studies or are weak studies, if in fact, that's not
17 clearly laid out to the provider, then they may be giving
18 information that isn't helpful to that patient.

19 So knowing how -- what those studies are and how strong
20 they are is incredibly important. Knowing what the background-
21 related risk is something that I think is really, really
22 important for the patient to understand that, no matter what,
23 pregnancy is risky, lactation is risky, and you've got to
24 understand what those risks are.

25 And then, of course, the benefit and risk considerations

1 to understand, is it better for you to take the medication or
2 not to take the medication? Is it better for you to provide
3 nutrition via nursing and lactation versus not to do that, and
4 what are the risks of not lactating, for example, right. And
5 that's not commonly -- it's certainly not included in the
6 labeling, but it's something that you've got to convey with
7 that patient.

8 And then medicolegal considerations and this risk of
9 liability, both for the provider and for the patient, are both
10 really, really important. So all of these aspects factor into
11 the decision making of a healthcare provider.

12 DR. BLALOCK: And just let me interject a comment sort of
13 in relation to this. You know, I think that some of the
14 information that is provided in the new labeling, like risk-
15 benefit, what is the, you know, risk among diabetes patients?
16 And we've heard a lot about mental health issues. What are the
17 risks if you don't take the therapy?

18 And I actually think a good thing about the new labeling
19 is at least there's an interest in trying to get some of that
20 information in there about, you know, those risks.

21 And the other thing that is new in the labeling is
22 providing information about the, you know, risk of
23 abnormalities as well as, you know, miscarriages, you know, the
24 baseline risk among people who are not taking the medication.
25 And I think both of those changes in the labeling are trying to

1 address, you know, B and C, at least the way that I interpreted
2 it.

3 So the next person on my list is Dr. Pleasant.

4 DR. PLEASANT: Thank you.

5 I'm not disagreeing with anything anybody said. Still,
6 these factors clearly all impact healthcare provider decision
7 making, which in itself isn't a complete statement because the
8 decision should involve the human being that's also in the room
9 other than the healthcare provider. But it, for example,
10 doesn't include economics. Just quickly, it doesn't include
11 culture.

12 Now, I guess you could say that you've subsumed culture
13 into risk perception, but I'd hate for that to actually be the
14 case because it deserves highlighting.

15 We can plain language the language that you're using
16 around the uncertainty all day long and come up with some
17 really lovely plain-language solutions, but plain language does
18 not guarantee an informed decision.

19 So part of the communication, as much as you might not
20 like this, so be it, has to include a process. We know how to
21 help people make informed decisions in the face of uncertainty,
22 but that's a process, not an explanation of the uncertainty.

23 So I would suggest that you be open to including that
24 science of the process of making an informed decision in the
25 face of uncertainty as part of the communication to healthcare

1 providers, to help that decision-making process in the room
2 between the doctor and the person. I'm personally trying to
3 ban the word patient, by the way, because who said you needed
4 to be patient to receive medical care?

5 Right. So there's a process there that we could talk
6 about and extrapolate quite a bit in addition to the plain
7 language of the uncertainty problem, how to explain the lack of
8 scientific data, which would probably actually -- I think that
9 would help you reach the ultimate goals that you're trying to
10 reach, because in a pithy way, remember, when there's a doctor
11 and another person in the room, there are two people with
12 problems.

13 DR. BLALOCK: Dr. Berube.

14 DR. BERUBE: A few things. First of all, I think one of
15 the answers to A is D. I mean, there's an order effect, which
16 we did a study on sunscreens, melanoma, and certain types of
17 ointments for Australia. And we discovered that if you talked
18 about the benefits before you talked about the risks, the
19 impacts were completely different, you know, with the audience.

20 And we just did a study in Singapore and the United States
21 on Chikungunya and on Zika viruses and vaccines, and the same
22 thing happened, right, where if you start with the benefit
23 factor before you go into the negative risk factor, what ends
24 up happening is, it re-contextualizes it.

25 It's almost like an anchor of a sort. You know, you're

1 giving them the positive message, and then when they take the
2 positive message and try to calculate the negative, they start
3 from where you started. Right. So they're starting at that
4 post and then working downward, which is always good for you.

5 I think the real challenge you have with this issue is
6 it'd be really nice if we can give you a confidence level to
7 each one of the approaches you're taking that would tell you
8 how the physician would interpret your message, but like as
9 Paul mentioned, the ideal way of doing this is with testing
10 more than anything else.

11 There is a strange source that I'll give you. There's a
12 professor of mathematics at Temple named Paulos who wrote about
13 innumeracy. And on page 127 of his book, he talks about
14 logarithmic safety indexes. And instead of doing the A, B, C,
15 X thing, he did a system like you would use for seismic
16 activity and towards indicating what type of, you know, of
17 earthquake you would get. And it's much more granular.

18 And when it's been tested, it sort of reduces the
19 exaggeration, hyperbole, people introduce into risk
20 estimations, because the granularity of it gives you much more
21 choices. Maybe that's something your physicians might like.
22 But if you're interested, Paulos's book is everywhere. It's
23 called *Innumeracy*, and it's a pretty good book.

24 But I agree the last thing was just contextualize all
25 this. You know, I spent years and years and years talking

1 about the risk of nanoproducts, the last 20 years collecting
2 data on this stuff, finally did a study which contextualized it
3 with the public. We found out the public thought on a list of
4 25 issues, it was 24. Right.

5 We sort of stepped back and went wait a minute. We had to
6 completely reexamine all the research we had done for years,
7 because if you look at it within context, it's really
8 unimportant.

9 And when you start in talking about all the variables that
10 go into a decision when a woman decides to have a child, I
11 think you're talking about a rich set of variables here that
12 can work quite effectively in contextualizing even the worst
13 risk, even the risk that would be on our REMS drugs.

14 But it has to start with people who have your problem,
15 whatever it happens to be, need to be medicated. And those who
16 are medicated benefit in this way. Is there a drawback? Yes,
17 there's a drawback, but if 100 women did what I'm advising, 97
18 of them would have healthy children. And it's really important
19 to do this. And we found it in vaccines, with Chikungunya and
20 Zika.

21 DR. BLALOCK: And I just want to make sure that I
22 understand. So you're saying that folks are more likely to
23 accept a risk if you start by describing the benefits and then
24 going into the risk in terms of the order? Is that what your
25 data suggest?

1 DR. BERUBE: It's a little bit acceptance, but it's a lot
2 of understanding.

3 DR. BLALOCK: Understanding.

4 DR. BERUBE: They're much better to understand the risk --

5 DR. BLALOCK: Understand.

6 DR. BERUBE: -- when they put it -- you start with the
7 positive implications rather than the negative. Rischiare is
8 Italian for circumnavigating cliffs. Right. It's not about
9 falling into the cliff; it's about circumnavigating it. And we
10 seem to have lost that.

11 DR. BLALOCK: Okay. Thank you.

12 Dr. Goldman.

13 DR. GOLDMAN: My comment relates to I guess E, medicolegal
14 considerations, and I'm just thinking about this through the
15 lens of what I do, which is, you know, as a neurologist, so not
16 someone that's committed to necessarily initially thinking
17 about caring about pregnant women, right, went into neurology,
18 but then take care of this disease, this population where
19 they're living with a disease during their childbearing years.
20 And we've seen -- I see tremendous variability on what patients
21 are advised about what to do.

22 And in the absence of their drug, they're at risk for
23 having a neurologic event that then completely handicaps their
24 ability to care for the child that they now have. So the
25 stakes are also really high.

1 And what I've sort of distilled down in thinking about
2 this today is in addition to thinking about risk and risk
3 tolerance and the risk tolerance of patients and how do we, you
4 know, put the language, but it's actually the liability. Who's
5 shouldering the risk?

6 So if a physician gives a medication, that physician is
7 shouldering all of the liability. If the physician withholds a
8 medication, the patient is now shouldering all of the liability
9 of the disease. And so the medicolegal implication here cannot
10 be ignored.

11 And so I think that -- and then you add in the fact that
12 there's no time. So if I have 5 minutes to meet with a woman
13 who wants a drug that has a unknown or uncertain risk, I'm just
14 going to tell her no, you can't have that and be pregnant;
15 that's not good for you. And now I have alleviated all of my
16 liability, and she walks out carrying the entirety of the risk
17 now.

18 So it's not just about risk perception, but it's about
19 who's shouldering the liability of any given risk. And I think
20 that has to be part of how we think about this in coming back
21 to importantly -- well, I guess that's all I'll say about this
22 portion.

23 DR. BLALOCK: Dr. Lyerly.

24 DR. LYERLY: So I have something to say, but I just wanted
25 to build on that first. I think part of it is liability, but I

1 also think it's responsibility. So whether or not there's a
2 risk of being sued, I think what we're really talking about is
3 who is ultimately responsible for the harm that would ensue
4 from the decision, right.

5 And so -- right. So I think patients look to their
6 doctors to partner with them in some way so that they can share
7 that responsibility. Providers, I think, are looking maybe to
8 the FDA to share that responsibility. And so I think, I just
9 think broadening that discussion to the notion of
10 responsibility and getting beyond these medicolegal
11 considerations and really think what's morally at stake for
12 people.

13 DR. GOLDMAN: This is Myla Goldman.

14 And this is an opportunity to help share that
15 responsibility from the FDA physician arrow.

16 DR. LYERLY: Yeah.

17 DR. GOLDMAN: Right, I think is key.

18 DR. LYERLY: Right, right, right. So that was my thought
19 just on that comment, but I also wanted to make a comment about
20 this list and just remind us that part of what is particularly
21 difficult here is the fact of pregnancy. So it's not that we
22 just have problems with risk perceptions or just have issues
23 with risk-benefit considerations, but that pregnancy makes all
24 of this stuff particularly difficult and in certain -- and in
25 many ways.

1 And one is that people do not like risk in pregnancy, at
2 all. And many years ago, like 25 years ago, a legal scholar,
3 Vanessa Merton, talked about this quixotic quest for zero risk
4 to the fetus, which is part of the reason that we don't have
5 any data in the first place, right. Nobody wants to impose
6 uncertainty or risk on pregnant women or fetuses. So the
7 researchers don't do it, so they shove it into the clinical
8 setting.

9 Another problem people have with risk in pregnancy is that
10 they notice the risks of intervention, but they don't notice
11 the risks of nonintervention. And I know that anybody who's
12 practiced around the room has been in a position where they are
13 trying to convince other providers who are not as used to
14 taking care of pregnant women that something is needed, an
15 x-ray, a medication, you know, an antiplatelet drug, whatever
16 it is, and that really ultimately, in the long run, this is
17 going to be best for the woman and her fetus, but it's hard to
18 get that intervention in place.

19 A third is that people are very uncomfortable with the
20 idea of trading off risks and benefits between really the two
21 entities that we're talking about. I hate to call pregnant
22 women an entity, but it's true. So here we have two entities
23 that these interventions will accrue certain risks and certain
24 benefits to one or the other, and they're going to be different
25 for those two. And there's a deep discomfort with making those

1 kinds of tradeoffs, and there isn't an agreed-upon way to do
2 it.

3 And so all of the data that's in the label is being
4 provided against a backdrop in which people are very
5 uncomfortable with and have distortions in reasoning about
6 risks in the context of pregnancy.

7 So I don't know exactly what to do about that, but I think
8 it's important to keep it in mind as we think about, you know,
9 what we're doing here and how best to do it. That's it.

10 DR. BLALOCK: Dr. Baur.

11 DR. BAUR: So -- this is Cynthia Baur.

12 So I actually see A through E very linked, based on what
13 we heard this morning. I think we got two answers about what
14 clinicians or prescribers, I guess to use your word, what
15 prescribers are doing. They're either defaulting to not doing
16 anything, right, to reduce the risk as much as possible to
17 zero, or they're giving conflicting information depending on
18 how they read the circumstances.

19 So in this tool that I mentioned before, one of the things
20 that we've put out there, taking a page from crisis and
21 emergency risk communication, is that it's really important for
22 the sake of clarity to talk about what you don't know -- what
23 you know, what you don't know, and what you're doing to find
24 out.

25 And I think what you're doing to find out is a really

1 important thing. So if you think about, you know, an emergency
2 response and the first person who stands up to talk about that,
3 that's what they're doing. It's like they're saying, you know,
4 we've had this outbreak, we've had this earthquake, we've had
5 this flood, we've had this whatever. This is what we know
6 about that. This is what we don't know, but this is what we
7 are doing to find out, and we will be back in a certain amount
8 of time.

9 So I think if we're talking about context, one of the
10 pieces of context that we haven't talked about that we've kind
11 of assumed is that both prescribers and patients even
12 understand the research that's underlying this and why it has
13 or hasn't happened.

14 So I think even backing it up a little bit more and
15 thinking about how that framing of what the research enterprise
16 is about, and I think we can do that in a clear and
17 understandable way, provides some context for understanding why
18 we don't have answers to some of these questions, why there is
19 such a high level of uncertainty. And in that context then,
20 what are the things that are known, what are the things that
21 are unknown, and what are the things that we're doing to find
22 out?

23 DR. BLALOCK: Dr. Cappella.

24 DR. CAPPELLA: So I want to agree with what was just said
25 because I think that is -- that's right on. I think there have

1 been two comments that might help contextualize the information
2 when there's maximal uncertainty to prescribers. And one set
3 has been identified by Dr. Berube in terms of benefits first,
4 the other by Dr. Baur associated with questions, with
5 information about the scientific process.

6 But there's a third component of context that could be
7 provided, although it may be too long to be provided, and that
8 is that Dr. Blalock made clear that there is a baseline
9 information -- there's a baseline level of risk to the fetus,
10 regardless of whether there's any drugs involved at all. And
11 that information is pretty clear. And so that information
12 helps to establish some of the scientific basis.

13 The other kind of baseline information that might help
14 contextualize what comes next might be the baseline risk to a
15 woman who is experiencing disease or negative consequences in
16 terms of her vulnerability and severity. And Dr. Wisner, this
17 morning, I think made a very interesting point about her
18 counseling sessions.

19 She says -- she said, if I paraphrase correctly, that she
20 begins her counseling session by telling the woman forget
21 about, for the moment, that you're pregnant and just consider
22 the consequences of the disease that you have and how we could
23 treat it if you weren't pregnant.

24 Again, that's clear-cut scientific information that helps
25 establish, I think, some of the science base for what then

1 comes next, which is here's what we don't know, and now we can
2 tell you about the pros and the cons of the information that is
3 out there.

4 So part of what I'm searching for is a way of -- and I'm
5 sort of pulling together some strands here. Part of what I'm
6 searching for is a way to ameliorate, mitigate the consequences
7 that come from maximal uncertainty with the next set of
8 information, which is we don't know how this drug is going to
9 affect a pregnant woman. There's pros, there's cons, there is
10 reliable, unreliable, robust, non-robust, consistent,
11 inconsistent information.

12 So I guess the big issue for me is how to mitigate, how to
13 ameliorate what comes next in the cases of maximal uncertainty.

14 DR. BLALOCK: And I think I probably do need to call us
15 for a close today. You know, I was given an option a little
16 bit ago of whether we wanted to stop right at 5 because the
17 cabs could have been, you know, brought at a different time,
18 and I said no, no, no, we're going to stop at 5. So we either
19 stop, or I'll walk back to the hotel.

20 (Laughter.)

21 DR. BLALOCK: So given that, great discussion. We'll come
22 back to this question. We've got a list of about six people
23 who have questions. So we'll start, you know, we'll pick up
24 right there tomorrow.

25 So I want to call the Committee, the FDA and -- oh, I want

1 to thank everyone, you know, for their contributions today.
2 And I call the meeting today for a close, and we pick up
3 tomorrow at 9 a.m.

4 (Whereupon, at 4:57 p.m., the meeting was continued, to
5 resume the next day, March 6, 2018, at 9:00 a.m.)

6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

C E R T I F I C A T E

This is to certify that the attached proceedings in the
matter of:

RISK COMMUNICATION ADVISORY COMMITTEE

March 5, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original
transcription thereof for the files of the Food and Drug
Administration.

TIMOTHY J. ATKINSON, JR.

Official Reporter