

Capital Reporting Company
Drug Safety and Risk Management Advisory Committee 12-12-2012

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FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (DSaRM)

Wednesday, December 12, 2012

FDA White Oak Campus, Building 31
The Great Room (Room 1503)
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland

Reported by: Rick Sanborn
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3 Kristina A. Toliver, PharmD

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs

7 Center for Drug Evaluation and Research

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10 Pharmacy

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13 University of Florida

14 Gainesville, Florida

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16 T. Mark Woods, PharmD

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19 Pharmacy Department

20 Saint Luke's Hospital

21 Kansas City, Missouri

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1 Elizabeth Conover, MSN

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4 Munroe-Meyer Institute

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12 Centers for Disease Control and Prevention

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15 John J. DiGiovanna, MD

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17 Dermatology Branch

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19 National Institutes of Health

20 Bethesda, Maryland

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3 Gynecology
4 Director, Asher Center for Research and Treatment of
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8 Psychiatry
9 Chicago, Illinois

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12 Associate Professor
13 Associate Division Chief
14 General Internal Medicine
15 Northwestern University
16 Chicago, Illinois

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1 GUEST SPEAKERS (NON-VOTING, PRESENTING ONLY)

2 Beth Choby, MD

3 Associate Professor

4 Department of Family Medicine

5 University of Tennessee Health Sciences Center

6 Memphis, Tennessee

7

8 Kate Ryan, MPA

9 Senior Program Coordinator

10 National Women's Health Network

11 Washington, District of Columbia

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13 FDA PARTICIPANTS (Non-Voting)

14 Mwango Kashoki, MD, MPH

15 Associate Director for Safety

16 Team Leader, Safety Policy and Research Team

17 Office of New Drugs (OND)

18 Center for Drug Evaluation and Research (CDER)

19

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1 Claudia Manzo, PhD

2 Director, Division of Risk Management

3 Office of Surveillance and Epidemiology (OSE)

4 CDER

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6 Gary Slatko, MD, MBA

7 Director, Office of Medication Error Prevention and

8 Risk Management

9 OSE, CDER

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11 Melissa S. Tassinari, PhD DABT

12 Acting Team Leader, Maternal Health Team

13 Pediatric and Maternal Health Staff (PMHS)

14 Office of New Drugs (OND), CDER, FDA

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16 Lynne P. Yao, MD

17 (Acting) Associate Director

18 Pediatric and Maternal Health Staff

19 OND, CDER

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

2 Call to Order and Opening Remarks Introduction of
3 Committee

4 DR. WINTERSTEIN: Well, this worked well. We
5 waited long enough, and there is total silence.

6 (Laughter.)

7 DR. WINTERSTEIN: Good morning. I would
8 first like to remind everyone present to please silence
9 your cell phones, Blackberries, and other devices if
10 you have not already done so. I would also like to
11 identify the FDA press contact, Ms. Lisa Kubaska. If
12 you're here present, please stand. Back there.

13 Good morning. My name is Almut Winterstein.
14 I am Acting Chairperson of the Drug Safety and Risk
15 Management Advisory Committee. I will now call the
16 meeting of the Drug Safety and Risk Management Advisory
17 Committee to order. We will go around the room, and
18 please introduce yourself. We will start with the FDA
19 and Dr. Gary Slatko, to my left, and go around the
20 table.

21 DR. SLATKO: Hello. I'm Gary Slatko. I'm
22 the Director of Medication Error Prevention and Risk

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1 Management in CDER.

2 DR. MANZO: Good morning. Claudia Manzo. I'm
3 the Director of the Division of Risk Management within
4 the Office of Medication Error Prevention and Risk
5 Management.

6 DR. KASHOKI: Good morning. My name is
7 Mwango Kashoki. I'm the Associate Director for Safety
8 in the Office of New Drugs in the Center.

9 DR. YAO: Hello. My name is Lynne Yao. I'm
10 the Acting Associate Director for the Pediatrics and
11 Maternal Health Staff in CDER.

12 DR. TASSINARI: Good morning. I'm Melissa
13 Tassinari. I'm a Senior Clinical Analyst on the
14 Pediatric and Maternal Health Staff, Office of New
15 Drugs, CDER.

16 DR. LIEBMANN: Jim Liebmann, Medical
17 Oncologist, University of Massachusetts.

18 DR. FRANCIS: Elaine Francis, with the
19 Sandcastle Toxicology Associates.

20 DR. SHAPIRO: Robyn Shapiro. I'm a
21 bioethicist and an attorney with Drinker, Biddle, and
22 Reath.

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1 DR. CRAGAN: Jan Cragan. I'm a physician
2 with the Birth Defects Branch at CDC.

3 DR. WHITAKER: Amy Whitaker. I'm a
4 gynecologist at the University of Chicago.

5 DR. CHAMBERS: Tina Chambers, and I'm an
6 epidemiologist in the Department of Pediatrics at the
7 University of California, San Diego.

8 DR. MADIGAN: I'm David Madigan. I'm the
9 Chair of Statistics at Columbia University in New York.

10 DR. MORRATO: Elaine Morrato, and I'm a
11 health services researcher in Health Systems Management
12 Policy at the Colorado School of Public Health.

13 DR. ERSTAD: Brian Erstad. I'm a professor
14 at the University of Arizona College of Pharmacy.

15 DR. TOLIVER: Kristina Toliver, Designated
16 Federal Officer, Drug Safety and Risk Management
17 Advisory Committee.

18 DR. WINTERSTEIN: As you heard, I'm Almut
19 Winterstein. I'm a pharmacist and
20 pharmacoepidemiologist at the University of Florida.

21 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz,
22 pharmacoepidemiologist at the Department of

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1 Epidemiology, Harvard School of Public Health in
2 Boston.

3 DR. WOODS: Good morning. My name is Mark
4 Woods. I'm the Clinical Coordinator and Residency
5 Program Director in the Pharmacy Department at St.
6 Luke's Hospital in Kansas City, Missouri.

7 DR. SUAREZ-ALMAZOR: Good morning. Maria
8 Suarez-Almazor. I'm a physician and a clinical
9 epidemiologist at the University of Texas MD Anderson
10 Cancer Center.

11 DR. KABOLI: I'm Peter Kaboli. I'm a general
12 internist at the Iowa City VA and the University of
13 Iowa.

14 MS. BROYLES: Susan Broyles, Patient
15 Representative, from Fort Worth, Texas.

16 DR. WISNER: Kathy Wisner. I'm a Perinatal
17 Psychiatrist and Director of the Mood Disorders
18 Program, the Asher Center, at Northwestern University
19 in Chicago.

20 MS. CONOVER: Beth Conover. I'm a genetic
21 counselor, and I coordinate a teratogen information
22 service at the University of Nebraska Medical Center.

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1 MS. WALDEN: Angelic Walden. I'm here as a
2 patient representative.

3 DR. DIGIOVANNA: John DiGiovanna. I'm a
4 dermatologist in the Dermatology Branch at the National
5 Center Institute, NIH, Bethesda, Maryland.

6 DR. RASMUSSEN: Sonja Rasmussen. I'm a
7 pediatrician and clinical geneticist, and I'm Medical
8 Officer and Deputy Director of the Influenza
9 Coordination Unit at CDC.

10 DR. GREENE: I'm Mike Greene. I'm an
11 obstetrician and Director of Obstetrics at
12 Massachusetts General Hospital.

13 DR. MENEFEE: Michael Menefee, Medical
14 Oncologist, Mayo Clinic, Florida.

15 DR. POLIFKA: Janine Polifka, Director of
16 TERIS, Department of Pediatrics, at the University of
17 Washington in Seattle.

18 DR. FINGERT: Dr. Howard Fingert. I'm the
19 Acting Industry Representative, and I'm at

20 Millennium: The Takeda Oncology Company, in
21 Cambridge, Massachusetts.

22 DR. WINTERSTEIN: And then we have Dr. Wolf

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1 on the phone. Would you introduce yourself?

2 DR. WOLF: Sure. I'm Michael Wolf. I'm an
3 epidemiologist and all services researcher and
4 Associate Division Chief for General Medicine and
5 Geriatrics at Northwestern University in Chicago.

6 DR. WINTERSTEIN: Thank you.

7 For topics such as those being discussed at
8 today's meeting, there are often a variety of opinions,
9 some of which are quite strongly held. Our goal is
10 that today's meeting will be a fair and open forum for
11 discussion of these issues and that individuals can
12 express their views without interruption. Thus, as a
13 gentle reminder, individuals will be allowed to speak
14 into the record only if recognized by the Chair. We
15 look forward to a productive meeting.

16 In the spirit of the Federal Advisory
17 Committee Act and the Government in the Sunshine Act,
18 we ask that the advisory committee members take care
19 that their conversations about the topic at hand take
20 place in the open forum of the meeting.

21 We are aware that members of the media are
22 anxious to speak with the FDA about these proceedings;

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1 however, FDA will refrain from discussing the details
2 of this meeting with the media until its conclusion.
3 Also, the committee is reminded to please refrain from
4 discussing the meeting topic during breaks or lunch.

5 Thank you.

6 Now Commander Kristina Toliver will read the
7 Conflict of Interest Statement. Conflict of Interest
8 Statement

9 DR. TOLIVER: The Food and Drug
10 Administration is convening today's meeting of the Drug
11 Safety and Risk Management Advisory Committee under the
12 authority of the Federal Advisory Committee Act of
13 1972. With the exception of the industry
14 representative, all members and temporary members of
15 the committee are special government employees or
16 regular federal employees from other agencies and are
17 subject to federal conflict of interest laws and
18 regulations.

19 The following information on the status of
20 this committee's compliance with federal ethics and
21 conflict of interest laws covered by, but not limited
22 to, those found at 18 U.S.C. Section 208 is being

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1 provided to participants in today's meeting and to the
2 public.

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

12 Related to the discussion of today's meeting,
13 members and temporary members of this committee have
14 been screened for potential financial conflicts of
15 interest of their own as well as those imputed to them,
16 including those of their spouses or minor children and,
17 for purposes of 18 U.S.C. Section 208, their employers.
18 These interests may include investments; consulting;
19 expert witness testimony; contracts/grants/CRADAs;
20 teaching/speaking/writing; patents and royalties; and
21 primary employment.

22 The Food and Drug Amendments Act of 2007

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1 requires FDA to bring at least annually one or more
2 drugs with Risk Evaluation Mitigation Strategies, REMS,
3 with Elements to Assure Safe Use, ETASU, before CDER's
4 Drug Safety and Risk Management Advisory Committee,
5 DSaRM. The Agency plans to present information on the
6 risk management of teratogens, some of which have REMS
7 with ETASU.

8 Today's agenda involves discussion of the
9 various strategies used by the Agency to define and
10 address teratogenic risk, including requiring REMS with
11 ETASU. The discussion will include an evaluation of
12 the different strategies and the decision framework for
13 selecting risk management strategies for teratogens.
14 The committee will discuss whether the risk management
15 strategies, including REMS with ETASU, assure safe use,
16 are not unduly burdensome to patient access to the
17 drug, and to the extent practicable, minimize the
18 burden to the health care delivery system. This is a
19 particular matters meeting during which general issues
20 will be discussed.

21 Based on the agenda for today's meeting and
22 all financial interests reported by the committee

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1 members and temporary members, no conflict of interest
2 waivers have been issued in connection with this
3 meeting.

4 To ensure transparency, we encourage all
5 standing committee members and temporary members to
6 disclose any public statements they have made
7 concerning the topic at issue.

8 With respect to FDA's invited industry
9 representative, we would like to disclose that Dr.
10 Howard Fingert is participating in this meeting as
11 industry representative acting on behalf of regulated
12 industry. Dr. Fingert's role at this meeting is to
13 represent industry in general and not any particular
14 company. Dr. Fingert is employed by Millennium
15 Pharmaceuticals.

16 We would like to remind members and temporary
17 members that if the discussions involve any other
18 products or firms not already on the agenda for which
19 an FDA participant has a personal or imputed financial
20 interest, the participants need to exclude themselves
21 from such involvement and their exclusion will be noted
22 for the record.

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1 FDA encourages all other participants to
2 advise the committee of any financial relationships
3 that they may have with the firms that could be
4 affected by the committee's recommendations.

5 Thank you.

6 DR. WINTERSTEIN: We will now proceed
7 with the FDA opening remarks from Dr. Claudia Manzo.

8 Opening Remarks

9 DR. MANZO: Good morning. I'm going to begin
10 this morning by stating that FDA uses several factors
11 in considering the selection of risk management
12 approaches for teratogens. However, there is no formal
13 policy or guidance on how FDA determines what
14 regulatory approach to take for teratogenic drugs, and
15 for that reason, the FDA approach may appear to be
16 inconsistent. So the objective of today's meeting is
17 to obtain the committee's viewpoint on a framework that
18 includes factors that FDA thinks should be considered
19 when selecting risk management approaches for
20 teratogenic drugs.

21 So there are generally two types of risk
22 management approaches that FDA takes. One is -- and

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1 this by far in the majority of cases -- most
2 teratogenic drugs are managed simply with approved
3 product labeling and various portions of the label. We
4 also have the ability to require sponsors to design and
5 implement, a risk evaluation and mitigation strategy,
6 or also termed "REMS". A REMS is a required risk
7 management plan that uses strategies beyond
8 professional labeling. The Food and Drug
9 Administration Amendments Act of 2007 provided FDA the
10 authority to require the sponsors to implement a REMS
11 when FDA determined that it's necessary to ensure the
12 benefits of the drug outweigh the risks.

13 A REMS can include a medication guide or a
14 patient package insert, a communication plan for health
15 care providers, Elements to Assure Safe Use, which I'll
16 describe a little bit in a slide or two, an
17 implementation system which would be required for
18 sponsors to ensure that certain elements have been
19 properly implemented, and a timetable for submission of
20 an assessment of the REMS.

21 So Elements to Assure Safe Use, or ETASU, are
22 medical interventions or actions that health care

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1 professionals execute when prescribing or dispensing
2 the drug to the patient. These actions may be required
3 in order for the patient to also continue treatment.

4 And depending upon the risk, the REMS may
5 require one or more of the following: that the
6 prescribers have specific training experience or are
7 specially certified; that pharmacists or other
8 dispensers are specially certified; that the drug can
9 only be dispensed in certain health care settings, such
10 as a hospital; that the drug be dispensed with evidence
11 of safe use conditions, such as laboratory test
12 results; that each patient using the drug be subject to
13 monitoring, or that each patient using the drug is
14 enrolled in a registry.

15 FDAAA requires that the Agency at least
16 annually bring one or more drug with REMS with ETASU to
17 the DSaRM Advisory Committee to solicit views on
18 whether the elements assure safe use of the drug, are
19 not unduly burdensome on patient access to the drug,
20 and to extent practicable, minimize the burden to the
21 health care system.

22 We're going to begin today with a number of

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1 FDA presentations. We'll begin with how FDA assesses
2 the risk of teratogenicity. We'll also provide a
3 summary of a retrospective review of CDER's risk
4 management approach to a subset of teratogenic drugs.
5 We'll also provide you a summary of what we know about
6 certain risk management strategies. I just do want to
7 point out that there is challenge in determining for
8 particular tools or risk management strategies, what
9 effect those individual tools have on the actual
10 patient outcomes.

11 This will be followed by a decision framework
12 for the management of the teratogenic risk, and then we
13 will finally have a presentation on an actual example
14 of a risk management decision.

15 Following a break, we'll have several
16 stakeholder presentations.

17 John Freeman will be presenting the industry
18 perspective on the management of teratogenic risk.

19 Dr. Beth Choby will be providing the
20 prescriber perspective on the clinical management of
21 non-pregnant females of reproductive potential who
22 require treatment with teratogenic drugs.

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1 with our presentations from the FDA. FDA Presentations
2 Evidence for Teratogenic Risk: Assessment of
3 Animal and Human Data

4 DR. TASSINARI: Good morning, everyone. My
5 name is Melissa Tassinari, and I am a member of the
6 Pediatric and Maternal Health Staff here in the Office
7 of New Drugs at CDER.

8 I'm going to start this morning with some
9 background on the sources in the assessment of data
10 that leads to the determination of a teratogenic risk.
11 For our discussions of the questions this afternoon, we
12 are going to be starting from the point at which we've
13 already made this assessment.

14 I also want to talk today about the patients
15 that are at risk and for whom specific considerations
16 for risk management must be made.

17 So I want to start with a fundamental concept
18 and a definition. The concept is the basis of the
19 field of toxicology, that all substances can be poisons
20 if present at an incorrect dose. The definition is
21 that of a teratogen, any substance, agent, or process
22 that interferes with normal prenatal development

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1 causing the formation of developmental abnormalities of
2 the embryo or the fetus.

3 When reviewing data for a product then, the
4 question becomes: When is a drug a teratogen?

5 To understand when a substance is a
6 teratogen, one can look at the principles that were
7 articulated by Dr. Jim Wilson. The first addresses the
8 fact that there is a gene environmental interaction
9 that can characterize the response to a potential
10 teratogenic exposure. Susceptibility varies with the
11 timing of any exposure, and teratogens act via specific
12 mechanisms that lead to the pathogenesis or resultant
13 birth defect.

14 The outcomes of a teratogenic exposure can be
15 described as one of four events: death, malformation,
16 growth retardation, and functional defect. The last
17 two principles concern the manner and degree of the
18 fetal exposure to the teratogen. Most exposures are
19 mediated by the placenta and are impacted by the
20 maternal disposition of the drug, and the likelihood of
21 abnormal development increases with an increase in the
22 dose to which the fetus is exposed.

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1 When gathering the scientific evidence to
2 assess teratogenic risk, a primary source of data is
3 the battery of nonclinical toxicology studies required
4 in a drug development program. These are designed to
5 identify hazards, assess potential toxic effects and
6 target organ systems, and estimate the safe starting
7 doses for clinical trials. They also assess hazards
8 that cannot be assessed in clinical trials; namely, the
9 potential for carcinogenicity and teratogenicity, and
10 to do that, we specifically look at the reproductive
11 and developmental toxicology studies. These studies
12 investigate the exposure of mature adults in all stages
13 of development, from pre-mating to sexual maturity.

14 The most common study designs are those that
15 are outlined in the International Conference on
16 Harmonization Guidance S5(R2). These are fertility and
17 early embryonic development studies, usually done in
18 the rat; the embryo/fetal development studies, usually
19 done in the rat and the rabbit; and the prenatal and
20 postnatal development studies normally done in the rat.

21 Those studies and that guidance are
22 accompanied by another guidance from the International

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1 Conference on Harmonization know as the Nonclinical
2 Safety Studies for the Conduct of Human Clinical Trials
3 and Marketing Authorization, or shorthand ICH M3(R2).
4 Importantly, in this particular guidance there are
5 statements as to when these trials should be conducted.
6 These reproductive toxicity studies can be performed at
7 any time but really must be performed before large
8 scale or long duration clinical trials can be
9 initiated. Both the reproductive toxicology studies
10 and the genotoxicity studies also must be completed to
11 include women of childbearing potential that are not
12 using highly effective birth control or whose pregnancy
13 status is unknown.

14 Within the FDA, reproductive and
15 developmental toxicity data are assessed in an
16 integrated fashion, as outlined in the guidance that
17 was issued in September of 2011. This provides a
18 consistent review of nonclinical data to estimate
19 possible human developmental or reproductive risks from
20 the nonclinical signals that you find.

21 There are two classes of this data:

22 reproductive toxicity data refers to the

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1 structure and functional alterations that could affect
2 the competence of the adult male and female animals
3 under study. So these are the fertility studies,
4 effects on parturition, effects on lactation.

5 Developmental toxicity refers to the adverse events on
6 the developing organism, and as I noted before, can
7 result in either mortality, dysmorphogenesis, that is,
8 the structural abnormalities that you see in birth
9 defects, alterations to growth, and functional
10 impairment.

11 These positive signals are evaluated to
12 estimate the likelihood of increased reproductive or
13 developmental risk in humans. This information is
14 considered in totality along with any general
15 toxicology data from human and animal studies,
16 including the pharmacodynamic and pharmacokinetic data
17 that is available at the time of the assessment. All
18 of these analyses account for not only the type of data
19 but also the quality of that data. Importantly, this
20 is a weight of evidence approach that is applied to
21 arrive to an overall conclusion for the reproductive
22 and developmental toxicity assessments.

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1 I know this is a busy slide, but as noted
2 earlier, these signals that have been identified from
3 the nonclinical studies are evaluated with respect to
4 the different factors and the assessment that can
5 result in an increased or a decreased concern for human
6 risk. For example, is there concordance? Has the same
7 or a similar signal been seen across multiple species?
8 Have multiple positive signals been observed
9 particularly at different stages of development or in
10 different classes of data, such as, have you had death
11 and have you had embryo-fetal malformations? Is there
12 a dose response? And how do the exposures at which the
13 signals were seen relate to the anticipated therapeutic
14 exposure that you are going to find in humans?

15 As all the available data are reviewed, an
16 overall evaluation of the potential for reproductive
17 and developmental toxicity emerges. These conclusions
18 are then communicated in the product labeling.

19 While the same data assessment and weight of
20 evidence processes are used to evaluate a biologic,
21 there are some differences that have to be taken into
22 account. Very often the standard designs, which I

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1 described previously, are not going to be applicable in
2 the adequate study of these types of drug products.
3 Species specificity or lack of specificity in a
4 traditional species requires alternative choices such
5 as a nonhuman primate. Rodents can often display
6 significant immunogenicity that limits the ability to
7 achieve the acceptable exposure for study. This is all
8 outlined and articulated in another ICH guidance for
9 the preclinical safety evaluation of biotechnology-
10 derived pharmaceuticals, S6.

11 So if we look now at human data, we know that
12 15 to 20 percent of recognized pregnancies will end in
13 miscarriage. We also know that there is a 2- to 3-
14 percent risk of a birth defect with every live birth.
15 We also know that for most causes, these are either
16 genetic or we have no idea why they occurred. And,
17 finally, we know that an exposure that results in a
18 pregnancy loss or a birth defect often occurs before
19 the woman even knows she's pregnant.

20 The agents noted here are examples of human
21 teratogens. The criteria for proof of human
22 teratogenicity follow the principles of teratology,

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1 meaning that the exposure to the agent occurred at
2 critical times in prenatal development. The
3 association of exposure and outcome should make
4 biological sense, and the confirmation of these comes
5 from well-conducted studies, delineation of clinical
6 cases, and, in some cases, supported by experimental
7 animal studies.

8 Human data rarely comes from planned clinical
9 trials. The adult clinical trials in a drug
10 development program are not designed or powered to
11 detect teratogenic risks, and very often these trials
12 are designed for either exclusion of a woman who is
13 pregnant, or discontinuation of that woman in the trial
14 if the pregnancy occurs during the trial. Importantly,
15 absence of signal in such clinical trials does not
16 exclude teratogenic potential. Human data comes more
17 often from observational studies.

18 For the prospective studies, the pregnancy
19 exposure registry being a key example, the important
20 aspect of these are that they are planned before the
21 outcome of the pregnancy is known. Depending on the
22 study's calculated power and the safety signal

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1 detected, pregnancy exposure registries may identify
2 how drug dose, timing of exposure, or maternal
3 characteristics affect the adverse outcomes.
4 Retrospective cohort studies collect data about
5 subjects after pregnancy outcomes are known and can
6 reveal associations between maternal drug exposure and
7 adverse pregnancy outcomes, but they do not by
8 themselves establish a causal relationship. Case-
9 control studies are useful because they have the power
10 to evaluate the association of a drug exposure with
11 rare events.

12 There are other sources of human data, and
13 those are the adverse event reporting systems,
14 published case reports, the FDA adverse events
15 reporting system itself, and there are database
16 studies, many of which have linked maternal child
17 records, they can be national registers such as those
18 that are found in Scandinavia and the United Kingdom,
19 and other studies, such as the Medication Errors and
20 Pregnancy Risk Evaluation Program, or MEPREP, and you
21 will be hearing more about these from Dr. Auth in a
22 later presentation.

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1 Once the assessment of the data has been
2 completed, the information will be included in the
3 product labeling. The current labeling follows the
4 publication of the Physicians Labeling Rule, or PLR.
5 The information for teratogenic risk can appear in
6 several sections, depending on the severity of the
7 risk. Focusing in on Section 8, the special
8 populations, Section 8.1 is the pregnancy section, in
9 which you are going to find a category letter
10 designation and required regulatory language, a
11 description of the risk and the available data, and
12 more recently, the labels contain the information in a
13 new and restructured format. The product labeling is
14 the first-line, first risk management tool, and it is
15 common to all products.

16 If you look at Section 8.1, what you're going
17 to find in that section is the mention of a pregnancy
18 exposure registry when it's present, importantly
19 including the contact information for that registry.
20 You're going to find a risk summary. In that risk
21 summary, there will be the letter category, but,
22 importantly, there will be an articulation of the key

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1 risk and data for the drug's effect, ordered as first
2 human, then animal, and if there is pharmacologic data,
3 that will be included. What you will also find in this
4 section are any clinical considerations that are
5 important for the decisions that are about to be made,
6 and that means that you're going to talk about the
7 aspects of the maternal disease, you're going to talk
8 about any pharmacokinetics that would indicate the
9 possible dose adjustments that might have to occur
10 during pregnancy or in the postpartum period. And you
11 might find in this section any effects that are known
12 in the perinatal period.

13 Subsequent to that will be two areas of data.
14 These data are the information that we used to provide
15 and construct the risk summary. Human data will be
16 ordered before the animal data.

17 Now, just to talk a little bit here about at-
18 risk populations. In order to make decisions about
19 managing a potential teratogenic risk, we need to
20 determine which population is at risk. An accurate
21 description of that population is important, not only
22 to ensure that all patients at risk are included, but,

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1 equally, patients who are not at risk are also
2 identified.

3 For questions of teratogenic risk, the
4 primary populations that are considered to be at risk
5 are pregnant women and females of reproductive
6 potential. While the category of pregnant women is
7 evident, the women and the adolescent who is fertile
8 and capable of becoming pregnant is a group that needs
9 some consistency in terminology.

10 Going forward, to describe this group, the
11 FDA has chosen to define females of reproductive
12 potential as girls who have entered puberty and all
13 women who have a uterus and have not passed through
14 menopause. This definition does not include age ranges
15 because of the variability in the onset and termination
16 of reproductive ability. We recognize, however, that
17 other terms have been and are in use to define this
18 risk group. It becomes important, therefore, to
19 understand the definition of the group being described
20 in any discussion of risk.

21 Recent product reviews and decisions have
22 raised concerns about another potential at-risk

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1 population. These are the female partners of male
2 patients, both pregnant, because of the potential fetal
3 exposure, and females of reproductive potential. The
4 scientific evidence in the process for evaluating the
5 potential for concern has been variable, and this is an
6 area where our thinking is now beginning to focus. And
7 we look forward to your conversations today to help us
8 in that discussion.

9 To complete the conversation, there are
10 populations who are not at risk, and those are the
11 males, females not of reproductive potential, meaning
12 prepubertal girls and postmenopausal women, and the
13 definition of menopause that is in use here at the FDA
14 is that menopause is after 12 months of spontaneous
15 amenorrhea or postsurgically.

16 So in summary, the scientific evidence is
17 considered from all sources in order to make this
18 assessment of teratogenic risk. It is an integrated
19 assessment.

20 Weight of evidence. Risk assessment for
21 teratogenicity relies on all available data at the time
22 it is made. For most circumstances when this

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1 assessment is first made, there are no human data. The
2 pregnancy section of the labeling is now evolving to
3 improve the communication of the risks and benefits for
4 consideration of product use, and the population at
5 risk helps define that risk management approach.

6 In the following presentations you will hear
7 how these factors, particularly the scientific evidence
8 and the defined at-risk populations, impact decisions
9 for the management of teratogenic risk.

10 Retrospective Review of FDA's Teratogenicity
11 Risk Management Approaches

12 DR. KASHOKI: Good morning. My name is
13 Mwango Kashoki, and I'm the Associate Director for
14 Safety in the Office of New Drugs.

15 Today I will present findings from a small
16 study that was performed to gather information about
17 what factors the Center has taken into account when
18 it's made its decisions about management of a drug's
19 teratogenic risk. My talk will describe how the review
20 was performed and its results. It will also provide
21 the background for the framework that the Center has
22 developed from that, and this framework is in regard to

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1 the management of teratogenic risks, and Dr. Vega will
2 be talking about that later on this morning.

3 Before I begin, I would like to acknowledge
4 Dr. Marilyn Pitts, who is on my team, for her
5 substantial contributions to this work.

6 So a framework is essentially a frame or a
7 structure that is composed of parts that are fitted and
8 joined together. CDER has been regulating drugs with
9 confirmed or potential teratogenic risk for decades,
10 and through its experience, the Center has developed
11 principles and regulatory practices that guide the
12 management of this risk. And with the Center's
13 progressive experience and more recently with increased
14 regulatory authorities with regard to risk management
15 decision-making, the Center is moving forward with more
16 formal documentation of these principles and regulatory
17 approaches. So we refer to the factors and
18 considerations that influence the selection of a
19 particular risk management approach for teratogenic
20 drugs as the framework.

21 We can think of risk management for
22 teratogenicity, and really risk management of any

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1 serious risk, as a continuum that starts with
2 adequately informing patients and providers about the
3 nature of the risks and what, if anything, they can do
4 to prevent, minimize, or manage the risk. For drug
5 products, the product label, which can include patient-
6 directed information, the product label is the
7 fundamental communication tool.

8 And FDA can also provide information about a
9 teratogenic risk using other communication vehicles
10 that it has available, such as our drug safety
11 communications or specific outreach to provider and
12 patient organizations. Further along the continuum for
13 teratogenic risk management are our REMS, our Risk
14 Evaluation and Mitigation Strategies. And depending on
15 the goal of the particular program, the REMS may focus
16 on provision of information to patients and providers
17 through targeted training or learning, or it could
18 include restricted distribution, and by restricted
19 distribution, I mean, limitations on patient and/or
20 provider access to the drug by requiring things like
21 enrollment or documentation of safe use conditions,
22 patient monitoring, or any other thing that is a

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1 prerequisite for being able to prescribe, dispense, or
2 have access to the drug.

3 Now, FDA has to take into account a lot of
4 decisions before it ultimately decides whether or not
5 it can approve a product. If a drug's risks outweigh
6 its benefits, then the drug won't be approved. This
7 slide shows some examples very generally of the types
8 of decisions that ultimately must come together into
9 the approve or not approve decision. FDA must
10 determine if there is sufficient evidence of benefit
11 and if there are serious risks associated with the
12 drug, and if there are serious risks, how should these
13 be addressed? Is labeling going to be sufficient to
14 address the risks, or do we need a REMS? All of this
15 is a very complex consideration that takes into account
16 not only the scientific data about the risk but also
17 important clinical and regulatory factors, including
18 the factors that are spelled out for us under the FDA
19 Amendments Act, or FDAAA.

20 Once we determine that a REMS is required, we
21 have then got to determine the goals of risk
22 management, and as I said before, depending on the goal

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1 of the program, you will have a more or less restricted
2 REMS.

3 So with regard to the review that was
4 performed earlier this year, we wanted to identify the
5 particular factors that contributed to the decisions
6 for the selected risk management approach to determine
7 if there were any considerations that influenced why
8 one particular approach was chosen over another. And
9 we were focused on factors that influenced whether
10 labeling was chosen as the risk management approach or
11 a REMS was added in addition to labeling.

12 In order to start our review, we selected a
13 small nonrandom sample of 17 known or potential
14 teratogens that had varying characteristics. To start,
15 the products had to have "strong" -- and I use this
16 word in quotes -- "strong" warnings for teratogenicity.
17 And we considered a product to have "strong" warnings
18 if it had a pregnancy category designation of either D
19 or X, and some teratogenicity-related information in
20 the boxed warning, contraindications, or warnings and
21 precautions sections of the labeling.

22 Now, as a reminder, under our federal

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1 regulations, a drug that is Pregnancy Category D is one
2 for which there are data from human investigations or
3 some postmarketing experience or other human studies
4 that have demonstrated evidence of fetal risk. However,
5 the potential benefits of using the drug in a pregnant
6 woman might be acceptable despite this potential
7 teratogenic risk. And a drug that is Pregnancy
8 Category X is one where there are animal studies and
9 human studies that show fetal abnormalities or there is
10 positive evidence of fetal risk based on human data.
11 And for products with a Pregnancy Category X, the risk
12 to the fetus outweighs the potential benefits of using
13 the drug in the pregnant woman.

14 In addition to this criterion of strong
15 warnings for teratogenicity, we selected products that
16 had a REMS, with the goal to manage the risk of fetal
17 harm from the product. We also selected products that
18 represented a range of therapeutic areas, such as
19 oncology and cardiology, and if you look in the
20 background material, you can see the other therapeutic
21 areas that were represented by the products.

22 We also selected products that reflected a

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1 range of patient populations and particularly different
2 populations of females of reproductive potential. And,
3 finally, we selected products that showed the range of
4 risk management approaches that we've taken over the
5 past several decades for teratogenic drugs.

6 The 17 teratogens in the study sample is
7 shown here, and also listed is the original approval of
8 the product and the current risk management approach,
9 and you can see that for some of the products that have
10 a REMS, they previously had a risk management program
11 that was referred to as a RiskMap. These RiskMaps
12 essentially had components that are equivalent to our
13 Elements to Assure Safe Use, and once the FDA
14 Amendments Act took effect, these RiskMaps were
15 formally approved as REMS. These REMS programs vary in
16 their goals and their elements and the way they are
17 implemented, but for the purpose of simplification and
18 for the study, they were just referred to collectively
19 as REMS.

20 So once we had identified our sample of
21 products, we then looked to see what information was
22 available about the teratogenicity risk management

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1 decision-making. We looked at the product labels, the
2 original label, current labeling, and any other kind of
3 labels that reflected over time changes to the
4 teratogenicity risk information. We looked at FDA
5 reviews that had been written around how to manage this
6 risk, identify and manage the risk, and we also
7 conducted a structured staff interview to get further
8 details about the decision-making. We looked at where
9 in the product label there was pregnancy and/or
10 teratogenicity risk information, and we really tried to
11 drill down into what people considered and how they
12 tried to put it together in order to ultimately come up
13 with their decision for risk management.

14 In our structured staff interviews in the
15 survey, we asked a multitude of questions, and you can
16 see that we asked about a lot of factors, everything
17 from the nature of the scientific evidence to how any
18 regulatory precedent might have impacted the decision
19 for risk management. We found that the narratives and
20 the reviews as well as the information that we obtained
21 through the staff interviews really provided the most
22 useful information. So the findings that I'm going to

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1 present represent the pooled qualitative data.

2 So what did we find? Consistent with what we
3 expected, we saw that several factors are considered by
4 the Center when we are making a decision about how best
5 to manage a drug's teratogenic risk, and we grouped
6 these factors according to certain themes that are
7 shown on this slide.

8 For example, the scientific evidence was
9 always a key consideration. The evidence around what's
10 the nature of the risk, what data do we have about the
11 product? Also considered was the medical condition
12 that was being treated, including the nature of the
13 population that that condition represented, the
14 clinical setting in which the drug would be used, and
15 anything that we have done prior with regard to
16 teratogenicity risk management in general and/or any
17 risk management decisions that we had made for products
18 in the class, if there was a drug class. And, finally,
19 we looked at, for the products in this sample, the
20 potential impact of the risk management approach.

21 So in the background materials we've detailed
22 the findings with regard to individual factors that

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1 were identified as considerations, but I want to
2 summarize here some overall five key observations about
3 how the factors were considered.

4 First of all, the scientific evidence was
5 always an initial factor in considering how best to
6 manage a risk, and that no single factor, in and of
7 itself, led to a particular risk management approach,
8 but, rather, the decision for risk management was based
9 on integration of all factors. Also, as we gathered or
10 obtained more information about the teratogenic risk or
11 the effectiveness of a particular approach for risk
12 management, the way in which a drug's teratogenic risk
13 was handled evolved over time.

14 We have also noted that over time the Center
15 is increasingly taking into consideration how much
16 providers already know about how to identify or manage
17 teratogenic risk or what are established practices
18 within the clinical setting that might be able to
19 inform or address teratogenic risk.

20

21

22 And then, finally, we also noted that

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1 decision-making for prior drugs in a class might shape
2 what teratogenicity risk management decision is made
3 for the next drug in the class.

4 Let me go through some examples to show you
5 what I mean. So with regard to the scientific evidence
6 being the fundamental or initial factor, let's take a
7 look at mycophenolate. This drug was initially
8 approved in 1995 and is used for the prevention of
9 organ rejection in adults with renal, cardiac, or
10 hepatic transplant, and it's used in combination with a
11 regimen of cyclosporine and steroids. Mycophenolic
12 acid is the active metabolite of mycophenolate mofetil,
13 but for the purposes of our discussion, these two drugs
14 are referred together as mycophenolate.

15 The reproductive toxicology studies that were
16 performed as part of the application for marketing
17 showed adverse fetal effects. And based on these
18 findings and in the absence of human data on human
19 outcomes, the product at time of approval was labeled
20 as a Category C drug, and there was no other risk
21 management strategy put in place beyond the labeling.

22 Now, around the mid-2000s, based on an

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1 assessment of postmarketing adverse event reports as
2 well as an evaluation of pregnancy outcome data from
3 the U.S. National Transplantation Registry, there was
4 new safety data to show a teratogenic effect in humans,
5 and so the pregnancy category was changed from C to D,
6 and it was determined that a REMS was necessary to
7 ensure that the benefits of the drug continued to
8 outweigh its risks.

9 An example of how decisions for risk
10 management are based on integration of all factors can
11 be shown by what was done for vismodegib. This drug is
12 approved for the treatment of metastatic basal-cell
13 carcinoma. It's a hedgehog inhibitor, and the hedgehog
14 pathway is important for embryonic development. There
15 were nonclinical reproductive toxicity studies that
16 showed things like severe midline defects, missing
17 digits, and other kinds of irreversible malformations.

18 Now, in addition to the scientific evidence
19 for teratogenicity, there were other factors that were
20 taken into consideration when thinking about how best
21 to manage this risk. For example, not only was the
22 medical condition, metastatic cancer, a consideration,

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1 but also the clinical setting in which the drug would
2 be used. This drug is obviously an oncologic drug, and
3 oncologists have familiarity with use of products that
4 have teratogenic risk, and within oncologic practice,
5 there is routine monitoring of patients, there are
6 conversations that have to occur around pregnancy
7 planning, and pregnancy testing is incorporated. So
8 all of these factors around the clinical setting
9 condition as well as the nature of the risk came into
10 play, and ultimately it was decided that labeling would
11 be sufficient to manage the drug's teratogenic risk.

12 In terms of how evolving data shapes the risk
13 management approach, isotretinoin is a very good
14 example. This drug many of you are familiar with,
15 approved in 1982, and is used for the treatment of
16 severe, recalcitrant nodular acne. And obviously
17 because of the nature of the indication, there are a
18 significant number of females of reproductive potential
19 in this population.

20 At the time of approval, the drug was labeled
21 as Pregnancy Category X, based on animal teratogenicity
22 information and expected high likelihood of adverse

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1 human outcomes. Also, at the time of approval, the
2 risk of teratogenicity was conveyed to providers in
3 terms of targeted kinds of risk messages. However,
4 over the years, there became issues with compliance
5 with the recommendations and the labeling, and the
6 language in the labeling was strengthened, and the
7 sponsor of the product at the time implemented a
8 specific risk management program that was aimed at
9 improving provider compliance with the labeled
10 recommendations.

11 Later on, because of ongoing reports of
12 adverse fetal outcomes following exposure, there were
13 additional labeling changes. And around 2000, because
14 of continued adverse event reports, the program was
15 strengthened, it became more restrictive, and
16 subsequently developed into the iPLEDGE program that
17 everyone, if not most people, know about.

18 I've already talked a little bit about how
19 knowledge about existing clinical practices and health
20 care provider knowledge can influence the risk
21 management decision, but here is another example to try
22 and highlight. Warfarin is one of the older drugs in

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1 our sample that was studied. It was approved in 1954.
2 And needless to say, it was challenging to get the
3 original documentation, forget about trying to find
4 anyone to talk with who might have been around at the
5 time of approval. But the initial labeling was based
6 on biologic plausibility, and the reproductive
7 toxicology studies have not been performed with this
8 drug, and at approval, there were no human data.

9 So around the late '60s, early '70s, there
10 were adverse event reports of adverse fetal outcomes
11 showing up in the medical literature as well as some
12 epidemiology studies that showed that exposure to the
13 drug during the first trimester caused a pattern of
14 congenital malformations. So with additional
15 information on this postmarketing information on
16 pregnancy outcomes, there have been several labeling
17 changes made for warfarin over time, including changes
18 to the pregnancy categories as well as enhanced
19 language about how to counsel patients about pregnancy
20 planning. Overall, it's been felt that with the
21 longstanding experience with this product and knowledge
22 about the risks, that established clinical practice

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1 really is sufficient at this time as well with the
2 labeled recommendations for risk management.

3 And, finally, let's look at how regulatory
4 decisions for products in the same class influence what
5 happens with a subsequent drug in the class.
6 Thalidomide was initially approved in the U.S. in 1998,
7 and I'm sure everyone is aware of this long
8 teratogenicity history with this product. Lenalidomide
9 is structurally related to thalidomide, and it was
10 approved in 2005. There were nonclinical reproductive
11 toxicology studies that showed evidence of teratogenic
12 risk, and based on these findings as well as the
13 relationship to thalidomide, lenalidomide was approved
14 with a RiskMap which was subsequently approved more
15 formally as a REMS, and the programs are similar.

16 So using information from our retrospective
17 review, the staff survey, as well as our more recent
18 experiences with teratogenic drugs and their risk
19 management, we identified the factors that comprise
20 this framework for teratogenicity risk management. I
21 show the factors here, and Dr. Vega will expand on them
22 in her talk.

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1 I do want to emphasize that this framework
2 shows only the considerations that FDA does and will
3 take into account when it's trying to figure out how
4 best to manage a teratogen's risk. This framework
5 isn't an algorithm, it's not a decision tree that leads
6 one to the risk management strategy, that's a different
7 but definitely related process and one that we think
8 will be informed by your discussion today.

9 So in summary, we have a lot of products that
10 are associated with teratogenic risk, and we found that
11 through our review that when trying to figure out how
12 best to manage this risk, we have to take into
13 consideration and integrate a variety of factors and
14 also that information about previous or existing risk
15 management approaches will inform what we do for the
16 next teratogen.

17 Teratogenic Drugs : Evaluation of the
18 Effectiveness of Risk Management Strategies

19 DR. AUTH: Good morning. My name is Doris
20 Auth, and I'm the Team Leader for the REMS Assessment
21 Team in the Division of Risk Management. Dr. Kashoki
22 just introduced the framework of factors that have been

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1 considered when determining an appropriate risk
2 management strategy for a teratogenic drug. My
3 presentation will move us past the approval of the
4 teratogenic drug to focus on the evaluation of the
5 effectiveness of the selected risk management strategy.

6 The goals of the presentation are to provide
7 insights on the effectiveness of different risk
8 management approaches to minimize teratogenic risks and
9 also to provide insights on the analysis of patient
10 access and health care system burden imposed by REMS
11 for teratogenic drugs.

12 I will first describe the types of
13 information that are required in order to evaluate the
14 effectiveness of a risk management strategy for a
15 teratogenic drug. Then I will provide a brief overview
16 of the REMS assessment processes before presenting data
17 that we have received from our REMS assessments for
18 teratogenic drugs.

19 I will also discuss some data sources other
20 than REMS assessments that may be used to inform the
21 effectiveness of a risk management strategy, such as
22 labeling alone.

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1 Finally, I will briefly discuss
2 considerations for the evaluation of patient access and
3 health care system burden that may be imposed by REMS
4 for teratogenic drugs.

5 So in order to evaluate the effectiveness of
6 a risk management strategy for a teratogenic drug, we
7 need comparable metrics for all drugs with teratogenic
8 potential. This includes the utilization of the
9 potential teratogen in females of reproductive
10 potential, also the number of pregnancies that may
11 occur in female partners of male patients treated with
12 a teratogen when this is felt to be relevant. We also
13 need to capture exposures to those teratogens and
14 outcomes of those exposures from the point of
15 conception to delivery and potentially beyond. And,
16 finally, we need to capture information on the
17 knowledge and behavior information of the stakeholders
18 involved, and this can be done through surveys or other
19 types of evaluations of knowledge and also through a
20 root cause analysis of any unintended pregnancies that
21 occur.

22 Before I present the data we have received

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1 from the REMS assessments, I would like to provide some
2 background on the type of information provided in our
3 REMS assessments.

4 The Food and Drug Administration Amendments
5 Act requires sponsors to submit assessments of their
6 REMS programs to determine if the goals of the program
7 are being met. For REMS with a communication plan
8 and/or a medication guide as the primary components,
9 this determination is made through the evaluation of
10 knowledge surveys supplied by the sponsors. For
11 example, prescribers and patients can be surveyed on
12 their knowledge of the risks of the drug as well as any
13 safe use conditions. And in addition, prescribers may
14 also be surveyed on their knowledge of proper patient
15 selection.

16 While knowledge surveys are also an important
17 component of most REMS programs with Elements to Assure
18 Safe Use, these REMS impose restrictions outlined in
19 Dr. Manzo's presentation, which allow for the
20 additional collection of information to inform the
21 effectiveness of the risk management strategy. This
22 includes information on REMS processes such as the

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1 adherence to the REMS requirements, as outlined in the
2 REMS document, and adherence to the safe use
3 conditions. It also may include utilization data such
4 as the demographics of the patients and prescribers or
5 the use in the population at risk. It also may include
6 information on outcomes, such as the number or rate of
7 events that the REMS is attempting to mitigate, and
8 also it may include a root cause analysis to determine
9 how or why the adverse event occurred.

10 There are currently nine REMS programs for
11 teratogenic drugs. Each program has at least one REMS
12 goal directed at the avoidance of unintended fetal
13 exposure, prevention of an unintended pregnancy, or to
14 inform stakeholders of the fetal risk. Seven of those
15 nine programs have submitted REMS assessments which
16 have been reviewed by the FDA. Of those seven programs
17 with assessments, the components include one program
18 that is a medication guide and communication plan
19 program, one REMS program which is communication plan
20 only, and five programs that include Elements to Assure
21 Safe Use. All of these ETASU programs also include a
22 medication guide as a component.

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1 All of the programs provide information for
2 both patients and prescribers on the teratogenic risks
3 and the safe use conditions. In addition, for the REMS
4 with Elements to Assure Safe Use, there is a
5 requirement for a negative pregnancy test to be
6 documented prior to dispensing the drug to a female of
7 reproductive potential. Some of the programs require
8 this documentation to be done by the prescriber, while
9 other programs will allow the patient to provide this
10 verification to the pharmacy prior to dispensing.

11 So this next slide shows the findings from
12 the knowledge evaluation for these REMS assessments of
13 teratogenic drugs, and although each program uses
14 slightly different methodology to obtain this
15 information, we see good knowledge of teratogenic risks
16 with a greater than 80-percent knowledge rate on the
17 risk demonstrated for both prescribers and patients. On
18 the other hand, we have seen lower performance or
19 knowledge rate for both patients and prescribers when
20 they are surveyed on the specifics of the individual
21 REMS program of recommended contraception that's found
22 in the REMS materials.

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1 So the next two slides, I'm going to be
2 presenting aggregate outcome data received in our REMS
3 assessments for these five REMS programs with Elements
4 to Assure Safe Use. Each program has been assessed at
5 least twice, and the information that I'm presenting
6 now does not include outcome information received
7 outside of these REMS assessments.

8 There have been approximately a quarter of a
9 million women treated with these five drugs through the
10 REMS programs. Approximately 187,000 of those are felt
11 to be females of reproductive potential, although I
12 would like to point out that each program does use a
13 slightly different definition for females of
14 reproductive potential. Of those 187,000, 335
15 pregnancies have been reported.

16 So across these five REMS programs, the
17 estimated pregnancy rate ranges from zero to 11
18 pregnancies per 1,000 females of reproductive potential
19 treated per year. In comparison, the estimated
20 unintended pregnancy rate from the U.S. population, the
21 most recent estimation from 2006, was 52 pregnancies
22 per 1,000 women using the age range of 15 through 44.

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1 It is difficult, however, to compare the patients that
2 we see in the REMS programs with the general U.S.

3 population, as we realize that some of the
4 illnesses that these patients are receiving these drugs
5 for may also impact or impair their ability to become
6 pregnant.

7 This slide further describes the outcomes of
8 those 335 pregnancies that were reported. The REMS
9 program assessments have reported 13 live births, 11 of
10 those were normal, 1 occurred actually in the partner
11 of a male patient. There have been two congenital
12 anomalies; however, we don't have any further
13 description of what those anomalies were. There have
14 been 29 miscarriages, two stillbirths, three ectopic
15 pregnancies, a total of 149 elective terminations. At
16 the data lock for the REMS assessments that we
17 evaluated, there were 44 ongoing pregnancies. An
18 additional 95 were coded as either unknown or lost to
19 follow-up. Those final two categories we may have
20 received some additional information on with the next
21 REMS assessment.

22 Though the REMS assessments obviously provide

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1 useful information, there are limitations to the data.

2 First, it is assumed there is underreporting
3 of pregnancies for a variety of reasons. I have listed
4 three on the slides: the patients or prescribers may
5 not be motivated to report; they may feel that the
6 reporting is unnecessary if the pregnancy has already
7 been terminated; and there may be some fear of
8 reporting the pregnancy when they're prescribing or
9 receiving these drugs through these restrictive
10 programs.

11 Information on specific outcomes may be
12 difficult to obtain for a number of reasons. The
13 patients may be unable to be reached, the patients or
14 prescribers. And we may be unable to actually
15 determine if the exposure occurred.

16 The ETASU REMS programs also provide valuable
17 information on the potential causes or reasons that the
18 unintended pregnancy occurred despite having all of the
19 safeguards of the restrictive REMS in place. Again,
20 each program uses slightly different methodology to
21 conduct their root cause analyses. Some use a third
22 party, others use a prescriber to obtain the

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1 information. So these interviews can be conducted over
2 the telephone or at a physician office visit.

3 The programs do have in common multiple
4 outreach attempts to the patient and the prescriber
5 prior to coding them as being lost to follow-up. Root
6 causes that can be identified from the ETASU program
7 include things such as systems problems. For example,
8 if a woman receives a teratogenic drug without having
9 that documentation of a negative pregnancy test and is
10 subsequently found to be pregnant, there would be
11 something that was wrong with the system. The women
12 may have a poor understanding of the recommended
13 contraception. They also may be noncompliant with the
14 contraception or they may just wish to become pregnant.

15 And, again, just as with the REMS assessment
16 data that we receive, the root cause analysis has very
17 similar limitations: we receive incomplete
18 information, there is very low participation, and
19 oftentimes the actual timing of the exposure is
20 unclear.

21 The most common root cause identified from
22 the data that we do have has been a failure of the

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1 patient to comply with the recommended birth control.

2 The other root cause identified has been contraceptive
3 failure.

4 So if we revisit this slide that I presented
5 earlier, we see that the REMS programs with ETASUs for
6 these teratogenic drugs do fulfill our wish list of
7 information. We have the utilization of the teratogen
8 and the population at risk. Some of the programs
9 provide data on pregnancies that occur in female
10 partners of male patients treated with a teratogen. The
11 programs are all equipped to capture exposures and
12 outcomes from conception to delivery, although, as I
13 mentioned a couple slides ago, we are aware of the
14 underreporting of pregnancies. And again all of these
15 programs capture knowledge and behavior information of
16 the stakeholders.

17 So without a restrictive REMS in place, what
18 sources of information are available to inform whether
19 labeling alone is effective at preventing pregnancy or
20 unintended fetal exposure to a teratogen? As Dr.
21 Tassinari described earlier, the source of information
22 may include pregnancy registry data as well as

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1 information from the medical literature. We also have
2 the FDA Adverse Event Reporting System, or FAERS, and
3 FAERS may be important at identifying a signal of
4 teratogenicity postmarketing.

5 There are other databases or surveillance
6 systems, and I would just like to mention a couple of
7 those. This is not an exhaustive list obviously. The
8 first of those is the National Birth Defect Prevention
9 Study, or NBDPS. This study uses interviews of mothers
10 of babies that are born with birth defects, and the
11 purpose of this study is to understand the cause of
12 birth defects, to identify new causes of birth defects,
13 and to develop programs to prevent birth defects.

14 Dr. Tassinari also briefly mentioned the
15 Medication Exposure in Pregnancy Risk Evaluation
16 Program, or MEPREP, and currently this program has data
17 on over 1 million mother-child links. This includes
18 information on all medications that were dispensed
19 throughout a woman's pregnancy. The purpose of this
20 program is to specifically study the effects of
21 prescription medications used during pregnancy.

22 Again revisiting that slide in the context of

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1 risk management programs that are not REMS, we see that
2 we can capture some of the information that we need to
3 evaluate the effectiveness of the strategy. What we're
4 not capturing is the bullet in blue, that is, we don't
5 have any information on the knowledge and behavior of
6 the stakeholders.

7 I would like to spend a minute or two
8 addressing the issues of patient access and health care
9 system burden imposed by a REMS, so I have repeated
10 this slide to remind us of this FDAAA requirement, to
11 receive input from the DSaRM Advisory Committee on
12 whether a REMS with Elements to Assure Safe Use does in
13 fact assure safe use of the drug, whether the elements
14 are not unduly burdensome on patient access to the
15 drug, and whether the elements, to the extent
16 practical, minimize the burden on the health care
17 delivery system.

18 So currently the REMS assessment that we
19 receive for the ETASU REMS programs do not attempt to
20 evaluate the impact of the program on patient access or
21 health care delivery system burden. Some of the
22 programs provide information that may be useful in

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1 achieving that goal, and these include programs that
2 report on their data from their call centers, so the
3 volume of calls that the center is receiving as well as
4 categories of the types of calls that they're
5 receiving.

6 We also receive records of shipment delays,
7 and these are for products that are exclusively
8 dispensed through specialty pharmacies. The reasons
9 that are provided for the shipment delays in the REMS
10 assessments make it difficult to determine whether the
11 delay was actually related to the REMS process or some
12 other pharmacy process. And currently we don't receive
13 any information on how many of these shipment delays
14 actually result in treatment interruption of the
15 patient.

16 The effect on patient access and health care
17 delivery system burden is very difficult to study in
18 all REMS programs, and the FDA will continue to explore
19 valid metrics for quantifying this consideration.
20 Stakeholder input will be sought at a public meeting in
21 2013.

22 So in conclusion, the data that I presented

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1 from the REMS assessments suggest that the REMS for the
2 five drugs with Elements to Assure Safe Use are meeting
3 the program goals. Although pregnancies have been
4 reported in all five of these programs, it appears that
5 the pregnancy rates are very low, even with the caveat
6 that there is probably some underreporting of
7 pregnancies. We also have evidence that the
8 prescribers and patients have a good knowledge of the
9 teratogenic risks.

10 It is very difficult to assess risk
11 management of teratogenic drugs without REMS or those
12 drugs that are risk managed with labeling only. We
13 just don't have any comparable data.

14 And, finally, further study is needed to
15 determine the appropriate metrics to evaluate access
16 and burden issues associated with REMS for teratogenic
17 drugs.

18 Framework for Decisions to Manage Teratogenic
19 Risk

20 DR. VEGA: Good morning. My name is Amarilyn
21 Vega. I'm a Medical Officer in the Division of Risk
22 Management, Office of Surveillance and Epidemiology. I

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1 will present the framework for decisions to manage the
2 risk of teratogenicity. The framework consists of a
3 compilation of factors considered by FDA when selecting
4 a risk management approach for drugs with teratogenic
5 risk. The framework is based on input received from
6 FDA reviewers and staff and is supported by findings
7 from the retrospective review presented by Dr. Kashoki
8 earlier today.

9 A female of reproductive potential may have a
10 medical condition prior to her pregnancy or may develop
11 a medical condition during pregnancy that requires
12 treatment with a drug with teratogenic risk. Depending
13 on the circumstances, fetal exposure could be avoided
14 by using other non-teratogenic products or by holding
15 treatment until after pregnancy ends. However, if
16 treatment with a teratogenic drug is necessary, it is
17 essential to consider the timing of drug administration
18 and to implement risk management measures. The goals
19 of the risk management approach would be to inform
20 patients and providers about the risks and safe use
21 conditions and to ensure the safe use of the product
22 through implementation of measures to avoid or minimize

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1 fetal exposure or to prevent unintended pregnancies.

2 The factors included in the framework can be
3 broadly categorized as intrinsic or extrinsic.

4 Intrinsic factors refer to those factors inherent to
5 the drug and teratogenic risk. Extrinsic factors
6 provide a context for drug use.

7 Intrinsic factors include the scientific
8 evidence of teratogenicity and drug-related factors.
9 Please note that certain drug-related elements may be
10 also categorized as extrinsic in nature. Extrinsic
11 factors also include factors related to the clinical
12 use of the drug, regulatory factors, and the
13 anticipated impact of a REMS.

14 This slide shows an outline of the framework
15 and will be the focus of this presentation and the
16 subject of FDA's first question to the panel. As FDA
17 gains experience in the regulation of drugs with
18 teratogenic risk and with the use of REMS tools, it has
19 become clear that in addition to the scientific
20 evidence of teratogenicity, other factors related to
21 the prescribing, dispensing, and use of a drug must be
22 considered in the selection of a risk management

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1 approach. Consequently, at this moment in time, the
2 Agency's approach to manage the teratogenic risk
3 includes weighing and integrating the data obtained for
4 each one of the factors included in the framework. I
5 will describe each factor and provide insight on how
6 reviewers consider these in managing teratogenic risk.

7 Let's begin the discussion with the two
8 intrinsic factors, the scientific evidence of
9 teratogenicity and drug-related factors.

10 As confirmed by the retrospective review, the
11 scientific evidence of teratogenicity is the initial
12 factor considered by FDA reviewers in the selection of
13 a risk management measure. As I just mentioned, the
14 selection of a risk management approach for
15 teratogenicity is context dependant, involving the
16 integration of the scientific evidence with data from
17 other factors in the framework. For this reason, the
18 risk of drugs with comparable scientific evidence of
19 teratogenicity may be managed differently.

20 The elements considered in the assessment of
21 the scientific evidence of teratogenicity were
22 discussed earlier today and include biologic

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1 plausibility, nonclinical data, and human data.
2 Documentation of biological plausibility is not
3 required to establish a causal association between drug
4 exposure and teratogenic effects. However, the
5 presence of a biologically coherent mechanism of action
6 strengthens the argument for a potential causal
7 association and may support the implementation of a
8 REMS. The scientific evidence of a product's
9 teratogenic potential derives from nonclinical data
10 generated primarily during the drug development process
11 and from human pregnancy exposures.

12 The guidance for reproductive and
13 developmental toxicities describes how nonclinical data
14 are integrated to estimate potential risk to humans.
15 The conclusions derived from the integration of these
16 data provide a starting point to the selection of a
17 risk management approach. The analysis of nonclinical
18 data may suggest, for example, that the drug does not
19 appear to increase the risk of adverse outcomes in
20 humans or that the drug may increase the risk of
21 adverse outcomes in humans or perhaps that the drug is
22 expected to increase the risk of adverse outcomes. It

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1 is critical to obtain a clear summary statement
2 characterizing the risk suggested by nonclinical data
3 given this information often provides the first
4 indication of the potential need for a REMS.

5 Nonclinical data suggesting or predicting an increase
6 in the risk of teratogenicity increases the level of
7 concern and immediately raises the question if a REMS
8 is required.

9 Findings from available human data may
10 supersede nonclinical data findings. Human data is
11 evaluated to determine if its quality and strength
12 support causality. Sources of human data include
13 clinical trials and postmarketing data. Clinical
14 trials are not designed nor powered to detect
15 teratogenic risks. A signal for potential
16 teratogenicity identified in a clinical trial is a
17 cause of concern and may support the implementation of
18 a REMS, while absence of a signal does not exclude a
19 drug's teratogenic potential and consequently does not
20 preclude the implementation of a REMS if other factors
21 considered in the analysis support the need for
22 additional risk management measures. Data from

1 postmarketing epidemiologic studies and
2 pharmacovigilance programs may help to further
3 characterize the risk and may support the revision of
4 previous risk management decisions. Confirmation of a
5 causal association may support the implementation of a
6 REMS.

7 Another important piece of information
8 obtained from human data is the nature of the
9 teratogenic effects. This is the frequency, severity,
10 and extent of the resultant disability. The background
11 rate in humans of the observed defect provides context
12 and a sense of the magnitude of the teratogenic
13 effects. The higher the anticipated fetal mortality
14 and/or morbidity associated with the teratogenic risk,
15 the higher the likelihood a REMS will be considered.

16 The second intrinsic factor is the nature of
17 the drug product itself. Intrinsic drug-related
18 factors include characteristics of the drug, the
19 efficacy, and the safety profile. The assessment of
20 efficacy and safety is typically conducted within the
21 context of clinical use. Therefore, I will discuss
22 these two elements in conjunction with other elements

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1 included under clinical use-related factors.

2 Is this drug first in class or is it a member
3 of a class with known teratogenic risk? Drugs which
4 are first in class pose the challenge of having limited
5 safety data, often requiring a more conservative risk
6 management approach until additional human pregnancy
7 exposure data are available. A drug in a class of
8 known teratogenic risk will likely have risk management
9 measures consistent with those implemented for other
10 members of the class.

11 A drug that can be self-administered or
12 administered orally poses the added risk of accidental
13 exposure and potential promotion of off-label use by
14 product sharing. Long-term therapy increases the
15 probability of fetal exposure during critical periods
16 of prenatal development. Therefore, a REMS is likely
17 to be considered for drugs with teratogenic risk that
18 are used for prolonged periods of time. But by the
19 same token, additional safeguards may be required for a
20 high-risk patient population receiving treatment with a
21 potent teratogen even if the exposure is limited to a
22 relatively short period of time.

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1 Now let's move on to discuss the extrinsic
2 factors included in the framework. As I mentioned
3 earlier, there are certain drug-related elements that
4 may be categorized as extrinsic in nature. Analysis of
5 drug utilization data provide information on how a drug
6 is being used in actual clinical practice. This
7 information is useful for postmarketing assessments, in
8 particular, for reevaluation of previous risk
9 management decisions and to identify patterns of drug
10 use, including off-label use.

11 Next the clinical use-related factors.
12 Clinical use-related factors include the
13 characteristics of the medical condition, the patient
14 population profile, and the context of medical care.

15 The characteristics of the medical condition
16 include the severity of the disease, the availability
17 and nature of treatment alternatives, the impact of
18 gaps in treatment, and the potential teratogenicity of
19 the medical condition itself.

20 The management of teratogenic risk associated
21 with a drug used in the treatment of a serious or life-
22 threatening disease in the mother must balance the need

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1 to prevent or minimize fetal exposure, the potential
2 for unintended consequences resulting from restrictive
3 REMS, and the need to implement a restrictive REMS to
4 maintain a favorable risk-benefit balance.

5 The decision to implement a REMS or not will
6 take into consideration the risk-benefit profile of a
7 drug with teratogenic risk in comparison to that of
8 other treatment alternatives. When there are no
9 alternative treatments that carry a lesser teratogenic
10 risk, a drug that is indicated for the treatment of a
11 life-threatening disease may have a less restrictive
12 risk management approach.

13 Once a drug has been started, what are the
14 consequences to the mother and fetus of gaps in
15 therapy? In general, if a gap in therapy may result in
16 a serious or life-threatening adverse outcome to the
17 mother or to the fetus, the use of risk management
18 tools that may result in treatment gaps is not
19 recommended. For example, drug use for the prevention
20 of organ transplant rejection should not have risk
21 management measures that may interrupt therapy since
22 this could result in loss of the transplanted organ.

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1 Some medical conditions, such as diabetes and
2 obesity carry a risk of teratogenicity. In such cases,
3 the process of selection of a risk management measure
4 must take into consideration potential adverse outcomes
5 of the medical condition itself if left untreated; for
6 example, increased maternal morbidity/mortality and
7 fetal loss and the potential benefits of treatment with
8 a product with teratogenic risk.

9 The next clinical use-related factor is the
10 patient population profile. What is the estimated size
11 of the population of females of reproductive potential
12 likely to use the drug? This is a difficult factor to
13 weigh and integrate in the assessment of need for a
14 REMS given its relevance is highly context dependent.
15 This table provides an example of the challenges
16 encountered in the assessment and integration of this
17 factor. The small size of the population at risk may
18 be considered a factor against the implementation of a
19 REMS with Elements to Assure Safe Use because of the
20 relatively small negative public health impact
21 resulting from teratogenic effects in a small group of
22 individuals, because of the potential limitations in

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1 access to the drug, and because of the burden imposed
2 on the health care system. However, the small size of
3 the population at risk may also be considered as a
4 factor in favor of a REMS with ETASU because a REMS
5 will prevent or minimize adverse fetal outcomes and
6 because of the relatively small burden to the health
7 care system imposed by a REMS targeting a small number
8 of patients and prescribers.

9 The potential for off-label use is always a
10 cause of concern. Anticipated extensive off-label use
11 may favor the implementation of a REMS. It is
12 difficult to predict patients' adherence to
13 recommendations for contraception, for example, since
14 this is not exclusively dependent on patients'
15 understanding of the risk but is also influenced by
16 their personal beliefs, sexual behavior, and attitudes
17 regarding medication use. Also, it is important to
18 determine whether the drug will be used by women who
19 are not planning a pregnancy but may become pregnant,
20 by women who are planning a pregnancy, or by women who
21 are already pregnant.

22 The context of care is increasingly playing a

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1 prominent role in the selection of a risk management
2 approach. The anticipated prescriber population
3 profile is key. How familiar are potential prescribers
4 with the medical condition being treated and with
5 identifying, monitoring, and/or managing
6 teratogenicity? The more familiar potential
7 prescribers are with the disease being treated and with
8 prescribing and managing drugs with teratogenic risk,
9 the less likely a REMS with elements to assure will be
10 required. The clinical setting of use may also provide
11 built-in safeguards with inpatient and specialized
12 clinic settings providing more access to medical
13 supervision than conventional ambulatory care.

14 The regulatory precedent for managing
15 teratogenic risk is always taken into consideration. It
16 is important to note, as mentioned earlier, that most
17 drugs with teratogenic risk, whether confirmed or
18 suspected, are managed through labeling only.

19 Frequently asked questions regarding the
20 regulatory precedent are: How has the Agency managed a
21 similar risk of teratogenicity with other products? And
22 how has the Agency managed the risk of teratogenicity

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1 of a drug used for different indications?

2 FDA is continuously learning from its
3 experience with existing REMS. Data collected through
4 the REMS assessment process, as well as data published
5 in the medical literature, contribute to our
6 understanding of the effectiveness of the REMS tools.
7 The Agency is in constant search for effective REMS
8 tools, and as science and technology advance, more risk
9 management tools are becoming available.

10 Finally, FDA considers the anticipated impact
11 of a REMS, including anticipated effectiveness and
12 potential unintended consequences. You just heard in
13 the previous presentation by Dr. Auth about the
14 challenges encountered in assessing the effectiveness
15 of the REMS for teratogenicity. However, the available
16 REMS assessment information is useful in guiding the
17 development of future REMS. The implementation of a
18 REMS with or without Elements to Assure Safe Use must
19 take into consideration the potential impact of the
20 REMS on patients and prescribers, for example,
21 limitations or delays in access to drug, and the
22 potential for adding a burden to the health care system

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1 that is not commensurate with the risk, including the
2 addition of redundancies in patient care.

3 In summary, the framework represents FDA's
4 concerted effort to document the principles guiding
5 decisions for managing teratogenic risk. This
6 framework consists of a compilation of factors
7 considered by FDA when selecting a risk management
8 approach. Factors will be added or removed to the
9 framework as science and risk management policy evolve
10 and based on the input from the panel today.

11 Once again, we want to emphasize that the
12 selection of risk management measures for drugs with
13 teratogenic risk is context dependent. No single
14 factor drives the regulatory decision for risk
15 management, and data for each factor are carefully
16 weighed and integrated before a risk management
17 decision is made.

18 These conclude my presentation. And next Dr.
19 Southworth will demonstrate the application of the
20 principles I just described as she presents an example
21 of a risk management decision for a product with
22 teratogenic risk.

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1 Examples of a Teratogenic Risk

2 Management Decision

3 DR. SOUTHWORTH: Good morning. My name is
4 Mary Ross Southworth. I am the Deputy Director for
5 Safety in the Division of Cardiovascular and Renal
6 Products. And this morning I am going to provide an
7 example of some of the factors we considered when we
8 made a risk management decision for a drug called
9 Letairis that I'm going to describe this morning.
10 Obviously, at the time that this drug was approved, we
11 did not have the formal framework that Dr. Vega just
12 presented, but you will see that we did make a lot of
13 the same considerations when we were deciding what risk
14 management approach to take with this drug.

15 I would like to remind the committee members
16 that the purpose of the presentation is not to revisit
17 the decisions that we made but really to illustrate how
18 the factors were used.

19 So, as I said, the example that we are going
20 to present this morning is called Letairis, or
21 ambrisentan. It's an endothelin receptor antagonist
22 that was approved in 2007 to improve exercise ability

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1 and delay clinical worsening in patients with pulmonary
2 arterial hypertension. Letairis was the second in
3 class. The first was approved in 2001; it was called
4 Tracleer, or bosentan.

5 At the time Letairis was approved, this class
6 of drugs, the ERAs, were thought to have two main
7 safety issues, and that was hepatotoxicity and
8 teratogenicity. Of note, the hepatotoxicity safety
9 issue with Letairis was reevaluated subsequent to its
10 approval, and that risk management plan has been
11 altered since then, and I'll describe that a little bit
12 later.

13 So the Letairis label at time of approval was
14 heavily modeled off of bosentan since it was the second
15 in class and displayed a lot of the same evidence for
16 teratogenicity that bosentan did. So Letairis carries
17 a Pregnancy Category X. It has a boxed warning which
18 states that it is contraindicated in pregnancy. There
19 is a need for women to use adequate contraception, and
20 there is a requirement for monthly pregnancy and liver
21 enzyme testing. That was at the time approval. And in
22 the label also is a description of what was found in

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1 the reproductive toxicity studies.

2 The REMS at Letairis approval was also
3 modeled after the Tracleer program. The REMS goals for
4 Letairis were to encourage informed benefit-risk
5 decisions, to minimize the risk of hepatotoxicity, and
6 to minimize the risk of fetal exposure and adverse
7 fetal outcomes in females of childbearing potential.
8 The REMS components for Letairis are all patients and
9 prescribers are enrolled when they're to use the drug.
10 There is extensive patient and prescriber education
11 about the safety risks. There is a medication guide.
12 And there are Elements to Assure Safe Use, primary of
13 which is a linkage of dispensing to monthly pregnancy
14 testing. It was also to liver function testing at the
15 time of approval, but that requirement has been
16 released.

17 So when we were making the approval decision
18 for Letairis, what did we consider when we were
19 determining how we were going to risk manage the
20 teratogenicity risk? Heavily weighted was the
21 scientific evidence of teratogenicity, which primarily
22 came from animal data. Animal models showed

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1 significant congenital anomalies, and these consisted
2 of abnormalities of the jaw and palate, blood vessels,
3 and thymus, that these were observed in rats and
4 rabbits. Pups displayed decreased survival, which
5 related to the inability to nurse. These anomalies
6 were seen at all doses tested of the drug, so No
7 Observed Adverse Effect Level was not identified. And
8 these malformations that were seen in these studies
9 were similar to malformations that were seen in
10 endothelin-1 knockout mice and animals treated with
11 other endothelin receptor antagonists, so fairly
12 convincing scientific evidence of teratogenicity.

13 One of the drug product-related factors we
14 considered was at the time of approval we knew that the
15 patients were going to need to have monthly liver
16 testing to minimize the risk of hepatotoxicity, so
17 adding on a monthly pregnancy testing for females of
18 childbearing potential seemed not to add to the burden
19 too much of the REMS.

20 Clinical use-related factors did also weigh
21 heavily in our decision. At the time of the first in
22 class, bosentan, this class of drugs represented a

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1 significant advance in the treatment of pulmonary
2 hypertension. Before that drug was approved, all the
3 treatments for pulmonary hypertension were parenteral
4 and required continuous central infusions of
5 prostanoids, so there was a lot of motivation to get
6 this drug on the market because there was a perceived
7 need for it.

8 There is also a substantial number of younger
9 females that are treated for pulmonary hypertension, so
10 we knew that there was a good likelihood that females
11 of childbearing potential would be among the treated.

12 The other clinical use factor that we
13 considered was that pregnancy itself in patients with
14 pulmonary hypertension, independent of any drug used,
15 is associated with significant maternal and fetal
16 morbidity and mortality mostly related to the changes
17 in hemodynamics that occur during pregnancy, which puts
18 significant pressure on the heart and circulatory
19 system so that treatment guidelines for pulmonary
20 hypertension discourage pregnancy and recommend
21 adequate contraception.

22 Regulatory factors also played a big part in

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1 our decision. As I had mentioned before,
2 teratogenicity was thought to be a class effect of the
3 endothelin receptor antagonists. And we considered
4 regulatory precedent to have been set at the time of
5 Tracleer approval in 2001, and at the time in the 5
6 years between approval of Tracleer, which is bosentan,
7 and Letairis, no formal assessments had been performed
8 that convinced us that the risk management approach
9 that was used in bosentan needed to be modified for
10 Letairis.

11 Just to illustrate that we do integrate new
12 data as experience in the REMS programs accrues,
13 several years after approval we did rereview clinical
14 trial data and postmarketing data related to the
15 hepatotoxicity of Letairis, and we concluded that the
16 risk of hepatotoxicity was similar between the placebo
17 group and the Letairis group from the trial data, and
18 the postmarketing study supported the fact that the
19 risk was probably the same for those two groups. So in
20 2011, we removed the warning in the label about
21 hepatotoxicity and also removed the requirement for
22 monthly liver testing from the REMS, but at this time

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1 all patients do continue to be enrolled in this REMS.

2 So in summary, the risk management decisions
3 for Letairis relied heavily on scientific evidence of
4 teratogenicity, characteristics of the medical
5 condition, the patient population profile, and
6 regulatory precedent.

7 Thank you.

8 Clarifying Questions for the Presenters.

9 DR. WINTERSTEIN: We will now have clarifying
10 questions from the committee for the FDA presenters.

11 I think I saw Dr. Morrato first.

12 DR. MORRATO: Thank you. These were very
13 nice presentations, so thank you. I had a follow-up
14 question for Dr. Auth. I enjoyed seeing the data that
15 you had where you were talking about pregnancy rates
16 under the REMS as well as comparing it to the U.S.

17 population. I'm wondering if there is any
18 data that looks at the pregnancy rates for drugs that
19 are teratogenic but that may not be regulated under
20 such restrictive REMS.

21 The reason why I bring that up, I know last
22 year when we were reviewing the Accutane package, there

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1 was some historical data there, and there was a paper
2 published in 1995 in New England Journal in which they
3 quoted with just more or less an educational directed
4 REMS and informed consent that the pregnancy rate was
5 3.4 pregnancies per thousand courses, and that fits
6 right within the range that you're citing for the more
7 restrictive. So I was just wondering if there is --
8 you know, I'm trying to understand where there is
9 return on incremental benefit of more restrictive
10 programs, et cetera.

11 DR. AUTH: I was not able to find that
12 information. The information from registries is, of
13 course, voluntary and very limited. I'm not stating
14 that the information is not out there, I just did not
15 come across that.

16 DR. MORRATO: Okay. Thank you.

17 DR. WINTERSTEIN: Just as a follow-up
18 clarifying question actually since this fits so well,
19 and I think it was Slide 10 in your presentation, Dr.
20 Auth, I'm not totally sure anymore, you mentioned that
21 the REMS that have an ETASU may have different
22 components in their assessment or there were three

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1 bullets, and one was basically knowledge and behavior,
2 and then there was one that mentioned specifically
3 pregnancy rates, and they were compared with an "or."
4 Is this it? Oh, no, this is not it. Hang on. Slide 6.
5 Yeah. So process utilization and outcomes, and those
6 bullets were presented with an "or" in between. So
7 just to clarify this, outcomes do not have to be
8 reported in a REMS assessment that has an ETASU; is
9 this correct? Or do they all have to?

10 DR. AUTH: They don't all have to be
11 included. This slide was just a general presentation of
12 the types of information that we may receive for REMS
13 with ETASU and not specific to the REMS for the data
14 that I presented for the teratogenic drug REMS.

15 DR. WINTERSTEIN: Dr. Erstad?

16 DR. ERSTAD: My question gets to I guess you
17 would call it inter-evaluator reliability, and it's I
18 guess for either Dr. Kashoki or Dr. Vega, and it was
19 with regard to the framework for the decisions to
20 manage the teratogenic risk. I notice that in the
21 survey that the conclusions were that the final
22 decisions were based on integration of a number of

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1 factors, and I guess it made me wonder if one or both
2 of you could maybe describe the process a little better
3 in terms of the number of people that are involved in
4 the decision-making and how it ultimately funnels up to
5 maybe a couple individuals to try to give me a better
6 feel again for this whole what I'll just call inter-
7 evaluator reliability. It seems like with different
8 people looking at this and different people are
9 obviously saying they took into account different
10 factors, I'm wanting to see what kind of consistency
11 there is with regards to different drugs being
12 evaluated by different people. So I guess a little
13 more about the process of how this goes up the ladder
14 with any given drug.

15 DR. KASHOKI: I can answer the question. This
16 is Dr. Kashoki, I'm sitting at the table. And then
17 others from the table can fill in if I miss anything.
18 So all of our reviews in the Center for Drug Evaluation
19 and Research are done by multidisciplinary review
20 teams, and the teams are comprised of persons who have
21 the relevant expertise to inform the discussion and
22 ultimately the determination. The way the office

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1 structure has been set up within the Center, certain
2 offices have designated authority to make the final
3 decisions.

4 So when it comes to, by and large, many of
5 the decisions around whether or not to approve a drug,
6 whether or not to make changes to an application, that
7 decisional authority lies in the responsible division
8 within the Office of New Drugs. So when we have an
9 application or a change to an application, a
10 multidisciplinary review team will be formed. When
11 there is an issue of teratogenic risk, this team can
12 include persons from the Office of Surveillance and
13 Epidemiology, everyone from the Division of Risk
14 Management, epidemiologists, and so on, as well as the
15 clinical staff within the Review Division itself that's
16 responsible for the product, and staff on the Maternal
17 Health Team within the Office of New Drugs.

18 Together these reviewers will look at the
19 information, bring their own perspective and their area
20 of expertise to the discussion, and make
21 recommendations ultimately to the person who has been
22 designated with authority to make the final decision.

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1 That person, based on the input from the review team as
2 well as their own senior management experience, will
3 ultimately make the decision for how to proceed with
4 the strategy. So it will be a team-based discussion
5 about the pros and cons and the various factors that
6 need to be considered when ultimately making whatever
7 decision needs to happen, including the one for
8 teratogenic risk management.

9 DR. ERSTAD: If I could have one quick
10 follow-up to that. So it sounded like it ultimately
11 funneled to this one person, who makes a decision, and
12 I guess then how many of those "one persons" are there?
13 Are there several people or does it really tend to be
14 just one person that it ultimately goes through?

15 DR. KASHOKI: Within the Office of New Drugs,
16 there are 17 review divisions, and so there will be one
17 person, the division director generally or their
18 deputy, who could make that decision within the
19 division. So depending on the review division, the
20 product, where it's been assigned, and therefore
21 following medical condition, et cetera, you will have
22 different people with different knowledge and

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1 regulatory and clinical knowledge ultimately being the
2 final decision-maker for an individual product.

3 DR. WINTERSTEIN: Dr. Menefee I think was
4 next?

5 DR. MENELEE: All right. So I have two quick
6 questions, and I'll direct the first one to Dr. Auth.
7 With respect to the 335 pregnancies that were observed
8 in those five REMS, do you have data regarding when
9 those pregnancies occurred during the REMS
10 participation? And more specifically, what I'm
11 interested in knowing, were any of those patients
12 subsequently found to be pregnant at the time that they
13 enrolled into the REMS?

14 DR. AUTH: The information that we do have
15 from those programs is generally first or second
16 trimester exposure. The programs are all designed to
17 prevent pregnancy when the drug is initiated. So I
18 don't have any information on that. I think the
19 information that was presented last year at the iPLEDGE
20 AC described how many of those pregnancies were
21 actually caught before the women began treatment.

22 DR. MENELEE: Okay. And then my second

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1 question was just more generic on the definition. And
2 you mentioned that there was some variability in the
3 definition of females of reproductive potential through
4 some of the different programs. I wanted to know, how
5 do you categorize females, adult women, that are
6 premenopausal that have had bilateral tubal ligations?
7 Do they fit into that --

8 DR. AUTH: Those women are considered females
9 of reproductive potential.

10 DR. MENEFEE: So they're still it. Thank
11 you.

12 DR. AUTH: Until they meet the age
13 requirement.

14 And, Dr. Tassinari, do you want to clarify
15 that for me? Did I state that correctly?

16 DR. TASSINARI: Yeah. There is specifically
17 no age requirement, it would be until the patient,
18 again, achieved menopause, so tubal ligation is not
19 considered.

20 DR. WINTERSTEIN: Okay. Dr. Madigan?

21 DR. MADIGAN: I'm sorry, this is yet another
22 question for Dr. Auth. I'm just trying to understand

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1 the 335. So you acknowledged that there can be
2 underreporting, of course, but do we have any handle on
3 how extensive that's likely to be? Or another question
4 in my mind is, does it vary across I guess it's seven
5 drugs? Does it vary according to the kind of severity
6 of the warnings that are provided? Do we have any
7 handle on the reliability of that number? I suppose is
8 what I'm asking.

9 DR. AUTH: That's really difficult to
10 pinpoint because, as you are aware, the iPLEDGE program
11 treats many, many more women than the other programs
12 that I described, those other four programs. There is,
13 of course, some variability, but, I mean, I can't
14 specifically say one is so much greater than the other
15 because of the differences in numbers of women treated.

16 DR. WINTERSTEIN: On follow-up on this, since
17 this data comes from registry, have there been any
18 formal evaluations on the generalizability of the
19 patients enrolled into that registry in terms of that
20 patients were actually subject to the REMS? So in
21 other words, the people who volunteered to participate
22 in the registry, are they in some way different from

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1 the people who have not volunteered to be in that
2 registry?

3 DR. AUTH: Well, let me clarify that. The
4 patients that are treated through the five ETASU REMS
5 programs, they're all enrolled in the REMS program, so
6 it's an all-or-none. It's not a voluntary
7 participation. If the women would like to receive
8 these drugs, they are all followed and their outcomes
9 are followed to the best of our ability as well as -- I
10 mentioned all of the issues with potential
11 underreporting. So this is not a voluntary registry.

12 DR. WINTERSTEIN: Okay. Dr. Fingert?

13 DR. FINGERT: Yeah. First I want to just
14 absolutely thank the Agency for this very scholarly
15 presentation. And so my question is really trying to
16 be constructive. I really have two questions. One is
17 starting with just stepping back a second. Dr. Vega's
18 Slide 19 about the framework -- I don't know if you can
19 easily show it -- but the question is, is this meeting
20 here, these 2 days, really intended to be the final
21 meeting for input and dialogue about this decision
22 about the framework, or really does the Agency view

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1 opportunities for continued dialogue with industry and
2 other stakeholders through other available venues?

3 I think we know there has been a series of
4 white papers published by organizations like the
5 Pharmacists Association about this topic, the Clinical
6 Trials Transformation Initiative, which the FDA and
7 industry and academics participate in, have been trying
8 to address some of these issues, and there may be some
9 room for alignment in approaches taken during the
10 conduct of clinical trials versus the conduct of
11 labeling. The BIO, which is a trade organization, has
12 expressed interest in holding telecons about these
13 topics. So I really want to know, the input we give
14 today, is that it, or is there an interest in continued
15 dialogue in coming months?

16 DR. MANZO: This is Claudia Manzo. I'll try
17 to address that question. We really consider this the
18 beginning of the discussion. We, just in general for
19 all REMS with ETASU, intend to seek input on when it's
20 appropriate to implement these sorts of programs, and
21 so we welcome all of the input, of course, that we're
22 going to be getting, but this, again, is a beginning

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1 discussion and we'll be having follow-up stakeholder
2 types of meetings in the next year or so, year or two.

3 DR. TASSINARI: Thank you. Just to follow on
4 and echo what Dr. Manzo was saying, I think there are
5 so many elements that we're going to discuss today that
6 one of the things that we certainly would like to hear
7 from you all are the areas where you feel specifically
8 we should extend this conversation beyond the meeting
9 for the 2 days.

10 DR. FINGERT: And then one other small
11 question. In Dr. Kashoki's presentation, Slide 7, this
12 survey that was presented I think deserves some
13 discussion later in the day because it may serve as a
14 precedent for others to copy and build on or not, a
15 foundational, or maybe not. And so I wanted to know if
16 Dr. Kashoki could give us more insights as to what is
17 meant by the sample selection criteria, small nonrandom
18 sample. I don't really understand what that means.

19 DR. KASHOKI: Sure. So we recognize that
20 there are scores, hundreds, of drugs that have language
21 about potential teratogenic effect, and we, in terms of
22 trying to prepare for this public discussion and trying

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1 to understand what extent of an evaluation we can do,
2 we thought about looking at the entire universe, but
3 that would have been almost impossible in terms of what
4 we were attempting to do in terms of methodology for
5 getting the information. So small, meaning to reflect
6 that we only looked at 17 of the possible scores to
7 hundreds of products that have potential or known
8 teratogenic effect.

9 We deliberately then just, you know,
10 from among our list of drugs that have teratogenicity
11 information, did not randomly select products. We were
12 deliberate in our choices mainly because we wanted to
13 solicit information about what factors come up when
14 you've got various therapeutic areas, for example,
15 various populations of females of reproductive
16 potential, and we really thought that we would get the
17 most knowledge where we had products that really had
18 substantial risk information related to them because
19 that would help us figure out where people had -- and

20 I'm using this in quotes -- the most concern
21 about teratogenic effect: What did they take into
22 account? So we were very deliberate, and so what's why

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1 it was really nonrandom and we were very thoughtful and
2 you could say unbiased in our selection of products.

3 We also wanted to make sure that we elicited
4 information about things that we expected to be fact
5 considerations. We knew going in what would likely be
6 thought of as part of the routine, we've been doing
7 this for some time now, and we wanted to confirm that
8 these factors were indeed being considered but also
9 begin to explore how people were putting them together
10 in terms of ultimately coming up with a decision about
11 what to do.

12 Dr. Chambers?

13 DR. CHAMBERS: Yes. I had a question for Dr.
14 Auth about the REMS evaluation, on the slide where you
15 presented information on evaluation of knowledge, and I
16 was just curious whether the lower performance on
17 specifics of recommended contraception both in
18 prescribers and patients, is that an assessment of
19 knowledge or an assessment of whether or not the women
20 complied with the recommendations for contraception?

21 DR. AUTH: In those cases, it's an assessment
22 on their knowledge, and we do acknowledge that there

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1 may be some confusion in the questions. They are asked
2 questions on contraception that may not include what
3 they're actually supposed to be using.

4 DR. CHAMBERS: Thanks.

5 DR. WINTERSTEIN: Dr. Cragan? Oh, Dr.
6 Shapiro. Sorry.

7 DR. SHAPIRO: I have two questions, I'm not
8 sure who they are for. But one relates to before we
9 get to the REMS recommendation and the nature of data
10 and the quality of the predictiveness of the animal
11 model and how that's taken into account or not, and
12 related to that, whether we're not really struggling
13 here with a lack of adequate data, and whether doing --
14 and this suggestion has a whole host of ethical issues
15 that are, of course, of interest to me, but doing more
16 research so that we're better armed to deal with this
17 issue that's on the table.

18 And the second has to do with enforcement and
19 enforcement discretion of the FDA, and what happens
20 when REMS are not complied with? And related to that,
21 whether there have been any legal challenges to some of
22 the limitations on access posed to potentially very

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1 important drugs on the part of pregnant women. We
2 know, of course, about the Abigail Alliance litigation,
3 which ultimately was not successful against the FDA,
4 but it was brought. We know about analogous case law
5 where pregnant women have wanted to have control over
6 their medical treatment despite the fact that they were
7 pregnant, and some of those have been successful,
8 although it's involved the right to refuse a C-section
9 or so forth as opposed to the right to access drugs
10 that they might need.

11 But I'm wondering if any of these issues have
12 been considered.

13 DR. TASSINARI: Let me see if I can try and
14 address the first question. And if I understand what
15 you were saying, you're expressing some or trying to
16 understand how we move forward, at least initially, in
17 what is often a situation where we are relying more
18 heavily on animal data than human data?

19 (No audible response.)

20 DR. TASSINARI: Okay. Well, as I noted
21 earlier, this is the primary source as we go forward,
22 and specifically the study battery is designed to try

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1 and maximize the amount of information that we get from
2 well-characterized animal models. So there is some
3 comfort in the data that we receive or that we get out
4 of those studies because we know well how to translate
5 that.

6 In the context of the adult human clinical
7 trials that are going on throughout the entire program,
8 can we make exact judgments? No. And that's why we
9 move forward with the best of our judgment, but I think
10 there is a degree of confidence that we have in the
11 system that is put forward at this point in time. This
12 is why the process is viewed as such an integrated one,
13 that we look for all possible data as we make those
14 final decisions about where our concern level is, at
15 least initially with the data that we have at hand.

16 Very often what you will find is that these
17 potential signals are ones where we still feel
18 comfortable that the drug may be approved, but we want
19 more information, and that more information comes in
20 the form of the postmarketing requirements, which is
21 where we will ask very often for a pregnancy exposure
22 registry or some other surveillance method that allow

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1 us to really try and gather some of that further data
2 to either confirm where we have made our risk judgment
3 or where we think we need to alter it. And I think you
4 saw through some of the examples today where we are
5 constantly trying to take the data as it comes in and
6 make sure that the risk evaluation that we have,
7 particularly for pregnant women, is accurate at that
8 time.

9 And to your second question --

10 DR. MANZO: With regard to -- I think
11 compliance was the question about what sort of actions
12 are taken for individuals that aren't compliant. So
13 FDA doesn't take any particular compliance actions
14 against prescribers, but companies, as part of the
15 implementation of the REMS, we'll take certain actions
16 if they become aware of prescribers, pharmacies, that
17 aren't complying with the REMS program, and it may
18 include as sort of a first step sort of reeducation
19 about some of the requirements of the REMS because
20 oftentimes it may be something that might not be an
21 intentional noncompliance, it might be something just
22 lack of understanding of what the requirements are.

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1 I think your other question was whether we're
2 aware of any -- maybe you can repeat the second
3 question, or the third question, that you had.

4 DR. SHAPIRO: Any legal challenges brought by
5 pregnant women or their doctors on account of limited
6 access.

7 DR. MANZO: I'm not aware of any.

8 DR. WINTERSTEIN: Dr. Suarez-Almazor?

9 DR. SUAREZ-ALMAZOR: Yes. I was wondering a
10 little bit about the role of industry in this. It's my
11 understanding that many of the REMS are actually
12 presented by industry and they have been accepted or
13 modified by the FDA. With this new framework, I'm not
14 entirely clear as whether the framework is going to be
15 used in the same way as before by the sponsors to
16 present a plan or if the idea is that some of these
17 REMS are going to be developed more in-house.

18 DR. MANZO: Well, FDA works very closely with
19 the sponsors, but these are programs that the sponsors
20 ultimately implement.

21 DR. SUAREZ-ALMAZOR: And that's not changing,
22 the mechanism, how the REMS will be proposed.

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1 DR. MANZO: Correct.

2 DR. SUAREZ-ALMAZOR: I mean, within the
3 framework, but I mean generally it will be the sponsor
4 who proposes a REMS but using the current framework.

5 That's --

6 DR. MANZO: Well, the requirement for a REMS
7 can be determined -- there can be a proposal that the
8 sponsor submits as part of an application, or if
9 they're aware of new safety information, so they can
10 make an initial proposal for a REMS, but FDA ultimately
11 makes a decision about whether or not a REMS is
12 necessary to ensure the benefits outweigh the risks.

13 DR. WINTERSTEIN: Dr. Morrato?

14

15

16

17 DR. MORRATO: Yeah. I had -- thank you -- a
18 related follow-up on that. So just to clarify, is the
19 FDA's intent on using the framework to retroactively
20 apply it across previous drugs or only for future
21 decisions and regulatory decision-making? So in other
22 words, to look at the whole class or all of the drugs

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1 that this is affecting so that there is consistency
2 applied, which I think is the goal of the framework. So
3 I didn't know if it's just future forward or if you'll
4 take a whole review of all the drugs affected.

5 DR. KASHOKI: In terms of determining for
6 each individual product what program or risk management
7 strategy is necessary to ensure the benefits outweigh
8 the risks, for those products that already have a REMS,
9 we would be able to look at information about the
10 effectiveness of what is currently available and then
11 make decisions about whether or not to modify the risk
12 management approach in the context of the factors that
13 we would reconsider it with additional information from
14 the REMS assessment.

15 We do have some regulatory threshold to meet
16 in order to make modifications to a REMS, so FDA must
17 meet those statutory requirements, which I'm going to
18 have to refer to someone else because I don't want to
19 misquote the statute, but we would have to first make
20 that determination, that the modification would be
21 necessary and the modification would be made in the
22 context of these factors that we're thinking about. But

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1 the plan is going forward to apply the same sorts of
2 thinking and factors in the framework for any future
3 programs. It's not necessarily that we're intending
4 that all products with teratogenic risk would have a
5 REMS, what we're trying to get at is, how best can we
6 use factors and apply these factors to make the
7 appropriate risk management decision for individual
8 products?

9 DR. MORRATO: Yeah, I was interpreting risk
10 management, the full spectrum that you gave in terms of
11 the label, the education, and then you had the ETASU.
12 So would it be therefore the responsibility of the
13 sponsors if they wanted to bring that dialogue with the
14 revised framework, that each individual one would have
15 to approach you and negotiate? Is that the intent --

16 DR. KASHOKI: They could, because we would
17 have to make individual decisions for applications, but
18 they could if they found that there was sufficient
19 information to do so.

20 DR. TASSINARI: I think it's important to
21 reiterate that what you see in the framework, the
22 content of the framework is not new. It may be new in

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1 the sense that we have put it together in the structure
2 that we are presenting today, but what was reaffirmed
3 by the retrospective look that we did do and the
4 example I think that you got from Dr. Southworth is
5 these kinds of questions have been asked all along, and
6 I believe they're asked not only by the FDA but also by
7 the industry that are going forward. So that allows us
8 to focus, as Dr. Kashoki is saying, on individual
9 considerations as they come forward.

10 DR. MORRATO: Yeah, I understand, but as
11 things evolve over time, the individual decisions can
12 become divergent, and it kind of relates back to the
13 comment on the inter-rater reliability, and that's, I
14 guess, for the later discussion.

15 DR. WINTERSTEIN: Dr. Francis?

16 DR. FRANCIS: My question is for Dr. Vega.
17 One of the extrinsic factors in the framework is
18 identified as the anticipated impact of the REMS and in
19 particular the anticipated effectiveness, and I think I
20 heard a statement that the assessment of the
21 effectiveness, that there aren't any performance
22 measures for this. So I guess my question is, how

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1 could you then account for what you would call as being
2 effective if there aren't any metrics to monitor the
3 performance and effectiveness?

4 DR. VEGA: Amarilys Vega, Division of Risk
5 Management. That is a very good point, and the fact
6 that we don't have an extensive body of information in
7 support of the effectiveness of REMS doesn't mean that
8 we look at the small amount of data that we have, and
9 sometimes more, sometimes less, but we do consider
10 that, and when we have any input, any information, on a
11 specific tool that we are planning to implement for a
12 specific product, then we obtain that data.

13 So you are correct. There is not a whole
14 body of information, as Dr. Auth described, in the REMS
15 assessment process, and there is not a whole lot in the
16 literature, but we do look at it, in the same way we do
17 look at the burden and the access to drugs. We
18 sometimes don't have a lot of information on that, but
19 we go through the process and consider that, and it's
20 included as part of the framework because it is one of
21 the aspects that we do consider, whether there is
22 sufficient information or not for that specific

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1 product.

2 DR. FRANCIS: Is there a plan to get this
3 type of information?

4 DR. VEGA: That is the ideal we are pursuing,
5 and we continue to look, as I've said, for sources of
6 information and for sources of REMS assessment
7 information, we do look for that, and for REMS tools,
8 too, because it's not only what we have, it's what can
9 be developed, so as technology improves and we have
10 more resources, we anticipate that this framework is
11 going to develop and be enriched by these new sources
12 that we can get hold of.

13 DR. WINTERSTEIN: In follow-up to this, and I
14 suppose that's to all the FDA representatives, I'm
15 curious, I think we all are curious about the
16 comparative effectiveness of various REMS approaches,
17 of course, and I appreciate the difficulty of obtaining
18 this data, but, of course, from a pharmaco-
19 epidemiological perspective, I'm starting to think
20 about, how could that be done? And one thing that
21 comes to mind is Phase 4 studies, I mean, large-scale
22 observational studies that could be made a requirement

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1 postmarketing to ascertain exactly this information,
2 you know, what was the percent of pregnancies that
3 occurred during exposure and what was the percent of
4 malformations or stillbirth and mortality and so forth
5 that occurred?

6 So I'm curious, in the data that Dr. Auth
7 presented, the Phase 4 requirements were not mentioned,
8 I'm curious, since that would really go across no
9 matter what kind of REMS would be used or whether it's
10 just labeling and no REMS, what is the typical
11 proportion where you require a Phase 4 study assessment
12 with respect to unwanted pregnancies and teratogenicity
13 in drugs that have a suspected risk for teratogenicity?
14 And have there been any considerations to use that to
15 get some kind of comparative effectiveness evaluations
16 of REMS approaches?

17 And then in follow-up on this, MEPREP was
18 mentioned, so, I mean, there are some larger databases
19 that the FDA is developing. Mini-Sentinal would be
20 another one. Are there any kind of approaches or plans
21 to use these types of databases to get some kind of
22 comparative effectiveness data?

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1 DR. AUTH: I would like to address your last
2 question about the use of the MEPREP database, and
3 currently -- I failed to mention in my presentation
4 that this data that is available from the MEPREP
5 database currently is a little old, it includes
6 information from 2001 through 2008, and currently the
7 Division of Risk Management has not accessed any of
8 this information to guide us on our risk management
9 programs. One of the problems with that is because
10 this information is not current, and hopefully we will
11 eventually have more data. The Division of
12 Epidemiology does have some studies that are being
13 planned to use this database.

14 DR. WINTERSTEIN: But not for the purposes of
15 comparative assessment of REMS.

16 DR. AUTH: No, not yet.

17 DR. WINTERSTEIN: And there is nothing with
18 Mini-Sentinal that has been discussed in that context
19 either.

20 Hi.

21 MS. PITTS: My name is Marilyn Pitts. And
22 Mini-Sentinal is a pilot of Sentinal, and it includes

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1 administrative claims data and also is a compilation of
2 multiple data sources. So we have thought about using
3 Mini-Sentinal, but our challenge now is trying to
4 identify codes that will actually successfully identify
5 the exposure to the outcome and also to link the
6 outcome to the mother. So we are actually working on
7 that as a priority, but we have not yet been able to
8 advance that.

9 DR. WINTERSTEIN: And I appreciate this is
10 obviously all very novel and starting to develop, so I
11 appreciate that there are thoughts about that.

12 MS. PITTS: Okay.

13 DR. WINTERSTEIN: Leaving the Phase 4
14 studies.

15 DR. TASSINARI: So just a point on your
16 question about, where do we get human data? And you're
17 right, what we do try and do is utilize the
18 postmarketing requirement opportunities that we have to
19 ask for the pregnancy exposure registries as
20 appropriate. This is always part of a conversation we
21 have when a drug is in for approval or even when a
22 supplement comes in and we feel that there is a

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1 significant reason to ask for that additional work. I
2 would just point out that those are not generally done
3 for comparative effectiveness purposes, they are
4 actually done to further understand and characterize
5 the potential safety and risks for that individual
6 product, and those are how those are designed.

7 I think, as a consequence, what you see is
8 our interest in these larger databases -- such as Mini-
9 Sentinal, such as MEPREP, and others -- that are
10 available to allow us to expand this information, and
11 then what our challenge becomes is understanding that
12 data in the context of what we already know about the
13 drug and then getting it into our communications
14 sources, and I am speaking primarily of the label.

15 DR. WINTERSTEIN: I mean, I understand that
16 these studies are individual, and for comparative
17 effectiveness, obviously that would mean that there
18 needs to be some compilation of the various results. I
19 was just wondering, how often do we actually have a
20 Phase 4 study requirement in the context of the
21 approval of a teratogenic drug? Is that standard? Is
22 it half of the time?

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1 DR. KASHOKI: I can't give you an exact
2 number. We can definitely go back and look at our
3 database and try and calculate a proportion if that
4 might be helpful, but it is not commonplace, I can say
5 that. It's not routine that a PMR might be required
6 even if a teratogenic risk has been identified for a
7 particular product. When these are required, it might
8 be as a PMR, or outcome evaluations might be done as
9 part of the assessment of the effectiveness of the
10 program, so it can be variable, but it is not frequent.

11 DR. WINTERSTEIN: Thank you.

12 Dr. Fingert?

13 DR. FINGERT: I just wanted to partly address
14 the question that was raised earlier about the industry
15 -- so I'm Howard Fingert, Acting Industry
16 Representative -- about the perspective of what
17 industry would be doing in this process. I do think
18 that the framework and the questions that we'll be
19 getting to later are really excellent, and from my own
20 personal perspective, the opportunity here to provide
21 more uniformity within the Agency and the people the
22 different companies work with and try to collaborate

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1 with is really a solid opportunity here because there
2 are some disconnects sometimes from one reviewer, one
3 division, to another, and bringing this into a common
4 agreed framework is important. That also helps with
5 efficiency, and we're all concerned about allowing
6 better efficiency in how we develop drugs at the
7 development stage, the marketing stage, different
8 stages.

9 But I wanted to turn it also into a question
10 about timing. Up till now there has been a bit of a
11 problem issue that some sponsors have raised about the
12 timing that seems in some minds to be limited by the
13 Agency to the REMS development and agreement, really
14 very, very late at the time of NDA review and filing
15 and acceptance, and from a practical reality, that can
16 be a problem because a small biotech, let's say, one
17 company was committed to a 4,000-patient study. For
18 its budget, to manage 4,000 patients, and then for all
19 patients in a relatively small kind of subset of
20 prostate cancer to get into that kind of study, it's
21 very hard to think about both the budget and enrollment
22 possibilities for other studies, for more innovation,

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1 for maybe some better studies that it could develop to
2 help address certain questions.

3 So the question to the Agency is, is this
4 work also going to allow earlier collaborative
5 decision- making about the REMS and the components and
6 the framework of REMS during the development process so
7 that companies would then just have more comfort to
8 know where they're going with their resources and with
9 their trials and what they're going to be needing to do
10 earlier in the process because of what is produced out
11 of this framework, in other words, well prior to the
12 time of NDA filing or prior to the times that now seem
13 to be in the perception of some somewhat of a
14 restriction as to when they have to hear about their
15 REMS requirements?

16 DR. SLATKO: So Gary Slatko. Thanks for
17 those comments. I think in the case of teratogenicity
18 obviously the signal for this phenomenon is happening
19 earlier in the development process than some of the
20 events that might only be detected during Phase 2 or
21 Phase 3 development. So I think there will always be a
22 desire for an early discussion of the teratogenicity

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1 issues as they emerge during animal toxicology studies
2 and the like.

3 In terms of more generally, the FDA's 21st
4 century review process as well as recent agreed PDUFA V
5 goals with the industry spell out an intent, a mutual
6 intent, to have earlier and more frequent conversations
7 about REMS program expectations, proposals, and
8 requirements beginning as early as the pre-NDA meeting
9 and repeating itself in the mid-cycle and late cycle
10 steps of the process. So whereas in the past, some of
11 those discussions may have been initiated later in the
12 review process, there is now an intention to
13 specifically address REMS-related issues and questions
14 many months earlier than perhaps it's happened in the
15 past, and we share the desire to provide more time for
16 earlier discussions about these topics during the
17 review process.

18 DR. WINTERSTEIN: Dr. Hernandez-Diaz.

19 DR. HERNANDEZ-DIAZ: I have a comment and
20 then a question, a comment regarding the use of new
21 data to modify a label and potentially the REMS. I
22 think it's great that FDA is trying to keep it flexible

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1 and incorporate new data that might come from databases
2 or registries to change the label and REMS accordingly.
3 However, I think that for new drugs that are coming to
4 the market, if we decide they might be teratogenic
5 based on toxicity or animal data or in some sense about
6 class effects, that might make it very difficult to
7 obtain further human data especially, of course. If
8 there are plans to limit fetal exposures and
9 contraceptive plans, then we will not capture use
10 through the databases or registries, especially given
11 the number of terminations that will come even if there
12 are exposures. Terminations are very hard to capture
13 in database studies. So if we assume teratogenicity
14 too soon, we might not be able to get further data. And
15 that was the comment.

16 And my question was regarding one of the
17 factors in the framework that was mentioned in the
18 review, was regarding the characteristics of the
19 medical condition. And I wonder if FDA can expand a
20 little bit on what has been done in the past, and
21 perhaps we are going to have opportunity to discuss
22 later today how best the characteristic of the medical

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1 condition affect the decision about the REMS, because
2 it was mentioned that if there is a need for the
3 treatment and the indication is very clear, that then
4 REMS will be considered; however, with the same
5 teratogenicity potential, if there is no need for
6 treatment, then labeling will be enough. So could you
7 explain a little bit on that factor, the characteristic
8 of the condition, how does that affect the decision for
9 a REMS or not?

10 DR. KASHOKI: You'll probably hate me at the
11 end of my response, but I'll say it anyway. When we're
12 talking about the characteristics of the condition, it
13 could be the relative seriousness of the condition. So,
14 for example, if a mother has epilepsy, and that is a
15 fairly serious condition and you would want to maintain
16 treatment, and it also could be the ability of the
17 condition itself to produce some teratogenic risk, and
18 then you will have to consider if you maintain
19 treatment with this product and it has a teratogenic
20 risk, what are the implications in that sort of
21 situation? Also raised when you're thinking about the
22 nature of the medical condition are, what are the

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1 available alternative therapies? What are their risk
2 profiles, their benefit profiles, and how does that
3 compare to what is under consideration right now? So
4 all of these kinds of characteristics that tie back to
5 medical condition.

6 Now, how they're put together, as Dr. Vega
7 said, can be context dependent because you will be
8 looking at, who is the female population that's being
9 treated and what is the context of care that is going
10 to be delivered?

11 So when we looked at that, we saw in the
12 review various ways in which this was approached, and
13 this is why we are posing the question back to you as
14 part of the afternoon discussion, is when you think
15 about this from your perspective, how does that play
16 into your thoughts about the direction in terms of risk
17 management, and how does that play into considerations
18 of other factors as well?

19 DR. WINTERSTEIN: We'll stop here in the
20 interest of time. There are a few more questions, and
21 we'll postpone them to the next round of questions that
22 the panel can ask. We will take a 15-minute break or

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1 10-minute break. Let's say we reconvene at 10:40.

2 Panel members, please remember that there
3 should be no discussion of the meeting topic during the
4 break amongst yourselves or with any member of the
5 audience. And we will resume at 10:40. Thank you.

6 (Break from 10:26 to 10:43.)

7 DR. WINTERSTEIN: I believe we had Dr. Hoeger
8 join after the first round of introductions. Would you
9 like to introduce yourself?

10 DR. HOEGER: Kathy Hoeger, Professor of
11 Obstetrics and Gynecology, Reproductive Endocrinologist
12 at the University of Rochester.

13 DR. WINTERSTEIN: Thank you.

14 We will now proceed with the industry
15 presentation.

16 Industry Perspective: Management of the
17 Teratogenic Potential of Drug Products

18 DR. FREEMAN: Thank you very much. Good
19 morning. My name is John Freeman, and I'm the Head of
20 Drug Safety and Risk Management with the
21 biopharmaceutical company Celgene. However, today I am
22 representing the pharma and bioindustry groups.

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1 I would like to thank the meeting organizers
2 for the opportunity to deliver this presentation, and I
3 would also like to thank and acknowledge the
4 biopharmaceutical manufacturers of products with
5 teratogenic potential that are the subject of REMS who
6 have provided contribution to the development and
7 review of this presentation.

8 From the outset, I would like to emphasize
9 that industry shares the Agency's objectives to promote
10 the safe use of drugs via appropriate means while
11 ensuring access and for ensuring that those means are
12 not unduly burdensome. As such, this meeting provides
13 an important opportunity for continuing dialogue around
14 REMS program operation, their effectiveness, and
15 opportunities for any further enhancement.

16 The next two slides I would like to share
17 with you and develop eight key messages based on our
18 collective experience so far. Fundamentally, these
19 acknowledge that there are opportunities for
20 standardization, however, this must be tempered with an
21 acknowledgement that there are differences between
22 drugs in terms of their benefits, their teratogenic

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1 potential, and the settings for their use that will
2 justify flexibility within any standardization. These
3 differences also contribute to defining different
4 approaches to risk management, whether that be through
5 labeling or more stringent REMS with Elements to Assure
6 Safe Use.

7 We also want to acknowledge the clear need
8 for stakeholder partnership early in a REMS programs
9 development to optimize design on the likelihood of
10 effectiveness.

11 Implemented programs will see many parties
12 participating in their operation. However, strong
13 leadership, clear governance, and accountability must
14 be present to ensure the continuing attainment of the
15 program's objectives.

16 In indicating a support for standardization,
17 it's industry's perspective that standardization will
18 be optimized through allowing time for consultation,
19 input, and very importantly, time to properly implement
20 the resulting guidance.

21 Also during this presentation we wish to
22 share some thoughts around creating better awareness

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1 amongst all stakeholders in terms of the performance
2 and effectiveness of REMS programs. This is
3 particularly important as REMS programs have the clear
4 potential to impact patient access to drugs. We feel
5 that this impact may be lessened through a combination
6 of stakeholder participation in program design and
7 implementation coupled with regular stakeholder updates
8 on operating metrics, both of which will help to
9 provide assurance that burden has been minimized in the
10 design. However, programs' benefits are the prevention
11 of burdens placed on society and the medical system
12 when individuals suffer birth defects. Thus, the
13 latter burden plays an offsetting role which is
14 important to consider.

15 Finally, and while not stated here, we also
16 wish to share some thoughts around the decision process
17 to determine risk management approaches to manage
18 teratogenic risk.

19 A starting point in discussing the management
20 of teratogenic risk is an appreciation that inadvertent
21 drug use in pregnancy is a significant possibility,
22 considering the path of all pregnancies are unplanned

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1 and fewer than half of these pregnancies are recognized
2 before the fourth week of gestation. This contributes
3 to the estimation made here, that about 64 percent of
4 women in the U.S. will be prescribed one or more drugs
5 during pregnancy inadvertently. This observation is
6 all the more significant considering the heightened
7 risk of embryo-fetal harm during the first trimester of
8 pregnancy.

9 As has already been described, the current
10 spectrum for risk management of drugs with teratogenic
11 potential ranges from labeling through REMS with
12 Elements to Assure Safe Use. Ninety-five percent of
13 products designated the current Category X are
14 addressed through labeling alone. The focus of the
15 current meeting is on REMS with ETASU and some of the
16 challenges that these create together with
17 opportunities to address those challenges. Given this
18 range of options around teratogenic risk management,
19 discussion is welcomed around decision-making within
20 the spectrum. Indeed, some suggestions will be
21 presented later in this presentation.

22 Fundamentally, it is important that we should

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1 continue to satisfy ourselves that the minority of
2 teratogenic drugs that are the subject of REMS
3 appropriately remain there.

4 Turning to the objectives and components of
5 risk management then, clearly the objective is the
6 avoidance of pregnancy exposure. This is achieved
7 through a concert of interconnected components that
8 collectively and individually address the objective.
9 These components include measures to promote an
10 understanding of the risk as well as practical
11 interventions such as contraception or the need for
12 abstinence and appropriately timed pregnancy tests. It
13 is also seen that each drug's specific characteristics
14 are also reflected in the need to incorporate elements
15 around the risks of drug presence in blood and bodily
16 fluids, and further, that sharing of drugs outside of
17 the REMS environment is discouraged.

18 Finally, whether it be through labeling alone
19 or REMS with ETASU, these methods seek to ensure
20 compliance prior to and at the time of dispensing.

21 This entire environment, this complex
22 interplay between the interests of patients,

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1 prescribers, and the unborn, is about achieving
2 balance, balancing the need for safe use of drugs in a
3 manner that doesn't interfere with patient access and
4 that doesn't introduce avoidable burden on an already
5 stretched health care environment. It's important,
6 therefore, that the stakeholders who design, manage,
7 regulate, govern, and participate within the programs
8 do so in an informed way.

9 More data and sharing of information around
10 three key areas should be pursued and disseminated:

11 firstly, the effectiveness of risk management
12 intervention, lessons learned in best practices; then
13 comes data around patients who may be denied effective
14 drugs due to perceived REMS barriers; and, thirdly, a
15 clear and comprehensive understanding of all of these
16 sometimes competing interests, the benefit of burden
17 appreciation. And all of this must be considered and
18 weighed against the backdrop of the impact of birth
19 defects were they to occur.

20 Stepping back and looking a little more
21 closely on the current risk management strategies, and,
22 first, labeling. Labeling remains the foundation for

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1 effective risk management. I mentioned earlier that
2 labeling is the primary risk management tool for 95
3 percent of current Category X products available within
4 the U.S. Labeling should be consistent with REMS
5 information and would logically be the starting point
6 for standardization around pregnancy testing and
7 contraception. It is recognized that the new pregnancy
8 and lactation labeling approaches help to provide a
9 greater level of detail around the risk of drug use in
10 pregnancy; however, this may not be well understood in
11 the transition from the current approach. It may be
12 helpful to consider a universal teratogen symbol for
13 use in the package insert carton and bottle label.

14 Turning to REMS as risk management, this is
15 where the majority of the discussion around burden
16 arises. Invariably, these programs require mandatory
17 pregnancy testing for defined patients, birth control
18 education and affirmation of use, enrollment and
19 education of participants, defined interactions between
20 prescribers and patients prior to prescriptions
21 followed by defined interactions between prescribers,
22 patients, and pharmacists at the time of dispensing.

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1 Measures of effectiveness may be built into
2 the risk management program via an early warning system
3 that sees any breakthrough pregnancies reported in real
4 time, and which is often augmented through the
5 establishment of a pregnancy registry.

6 Once these elements are defined, a
7 comprehensive and fully resourced implementation has to
8 be enabled to permit a REMS with ETASU to address its
9 objectives. For industry, this quickly becomes a very
10 large complex project that continues through the
11 product's life.

12 A REMS implementation system involves a
13 complex network of people, processes, and technology.
14 The starting point is a central database of certified
15 participant entities. A transactional process is used
16 to address the program's elements, and in doing so,
17 permits compliance with operating standards to be
18 monitored.

19 In addition, this ongoing quality
20 control/quality assurance of the role played by
21 pharmacists is achieved through onsite auditing.
22 Performance metrics are often built within these

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1 systems to ensure that prescriptions are filled within
2 defined timelines. These systems must remain
3 responsive to customer needs and have the ability to be
4 modified to enhance the customer experience. A good
5 example is to enable access to the systems via phone,
6 fax, and online. All of the above are codified within
7 written operating procedures to ensure proper
8 governance control and the regular evaluation of the
9 effective implementation of the system.

10 Not to detract from the impact of these
11 programs on participants, the level of commitment by
12 industry in these programs has to be considerable to
13 ensure the attainment of program objectives, not just
14 at the time of implementation but throughout the
15 program's operation. This includes, but is not limited
16 to, creating a governance structure to monitor the
17 correct deployment on operation of the program,
18 allocating and adjusting resources to meet the
19 program's needs, establishing clear process, and
20 ensuring ongoing quality assessment.

21 What is clear is that these programs cannot
22 operate in a vacuum and that they benefit from periodic

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1 stakeholder input with a view to maximizing their
2 benefit and minimizing their burden. Today's meeting
3 is one such opportunity to secure stakeholder input,
4 and there may, for example, be opportunities to
5 introduce aspects that may be standardized which may
6 contribute to both burden reduction while augmenting
7 effectiveness potential.

8 We would like to share observations around
9 two definitions and two operating standards in the
10 following slides. The following four slides examine
11 some of the differing definitions and standards that
12 exist within the nine products possessing teratogenic
13 potential, which are the subject of REMS programs,
14 seven of which include Elements to Assure Safe Use.

15 The first of these is the definition of
16 females of childbearing potential or reproductive
17 potential, the primary target risk group. At a glance,
18 it is evident that this definition is inconsistent
19 across these nine programs. There are inconsistencies
20 between the programs in the definition of sexual
21 maturity and in the period of time postmenopause that
22 the definition applies, 12 months postmenopause, 24

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1 months, or no specific time period at all. Some
2 programs offer no definition of a female of
3 childbearing potential.

4 Given the fundamental importance of this
5 particular definition, the absence of consistency is
6 quite striking. Additionally, as this definition may
7 drive adjustments to ETASU requirements based on
8 patient risk group, this also has a potential impact on
9 participant burden.

10 By the same token, explicit definition of
11 females not of childbearing potential are also
12 inconsistently represented; 5 programs offer
13 definitions and 4 do not. It should be recognized that
14 though these definitions may be specific to the
15 anticipated patient population, for example, if drugs
16 are used exclusively in adults or an oncology setting
17 where chemically induced menopause is common, and other
18 considerations apply. Whether it be the definition of
19 females of childbearing potential or females not of
20 childbearing potential, standardization could be
21 helpful and could be reflected both in labeling and in
22 REMS. In doing so, it could play an important role in

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1 reinforcing areas of focus for prescribers.

2 Pregnancy testing standards also display
3 variation across the nine programs, but there may be
4 greater scientific justification for these differences.
5 Factors such as the probability of exposure resulting
6 in fetal harm and the time window for risk exposure
7 coupled with the anticipated use of a drug as either
8 chronic or acute contribute to a need for
9 individualization of approach. Nonetheless,
10 opportunities for standardization are worthy of
11 exploring if an adjustment of pregnancy testing
12 approach can be achieved without increasing risk
13 potential. My earlier remarks around the majority of
14 pregnancies being unplanned and unrecognized before the
15 fourth week of gestation have a big bearing on this
16 element.

17 Then to contraception, one of this meeting's
18 stated objectives for discussion. Here again, we
19 observe inconsistencies in the way that these nine
20 programs approach contraception. There is variety in
21 the number of types of contraception that are
22 recommended, and although not shown here, there is also

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1 inconsistency in how contraception is categorized in
2 respect to its efficacy. Some programs specify
3 requirements for male patients, while most do not.

4 The current array of contraceptive
5 requirements have been heavily influenced by product
6 and teratogenic risk-specific factors. Current

7 Category X products have more clearly defined
8 requirements than non-Category X. The level of
9 teratogenic risk associated with each product has also
10 influenced contraception: the greater the perceived
11 risk, the greater the perceived need for contraception.
12 Also, too, the individual drug's risk also influence
13 contraceptive options. For example, a teratogenic drug
14 that also carries thrombotic risk would need to have a
15 different list of recommended oral contraceptives.
16 These differences aside, there are possible
17 enhancements to the way that contraceptive standards
18 are expressed within REMS programs.

19 Beyond definitions and operating standards,
20 we would like to encourage discussion around
21 effectiveness measures. It has become apparent that
22 participants who have played a role in shouldering

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1 these programs' burden haven't had a full opportunity
2 to understand if that burden is offset by program
3 benefit. Broadly speaking, there are three types of
4 measures of effectiveness that are utilized, and
5 remember that these revolve around a single common
6 objective within these programs, the avoidance of fetal
7 exposure. The three methods include objective
8 assessment of endpoint attainment, i.e, pregnancy
9 occurrence and the outcomes of those pregnancies;
10 compliance assessment against the program's standards
11 and procedures; and measures of understanding and
12 knowledge retention around the risk.

13 So here are a few practical suggestions: One,
14 pursue standardization of effectiveness determination
15 across programs; two, augment this acquisition of data
16 with assessments of the impact on patient access to
17 understand whether patients are being denied drug
18 access on account of REMS, and if so, why; and,
19 thirdly, seek to share these assessments within the
20 stakeholder and participant group as a means of
21 fostering REMS engagement and support.

22 So turning now to a different topic, that of

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1 determining optimal approaches to teratogenic risk
2 management for a given teratogen, there are at least
3 five categories in the assessment and decision-making
4 process that need to be evaluated, and they are
5 summarized here: the disease setting, the nature of
6 the anticipated and unanticipated treatment population,
7 the drug's benefit, the probability and nature of the
8 teratogenic risk, and the time window in pregnancy when
9 risk is most critical.

10 So let's walk through each of these in a
11 little more detail. Firstly, the nature of disease.
12 Seriously ill patients may justify different risk
13 management approaches than the less seriously ill.
14 Equally, drugs used in acute life-threatening
15 situations may necessitate different practical
16 approaches to risk management than in chronic
17 situations. Disease prevalence has a bearing. It
18 would be easier to effect risk management within a
19 small discrete identifiable group of prescribers than
20 in a situation of high prevalence. And then the
21 disease itself may influence both reproductive
22 potential and the likelihood of sexual behavior.

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1 At the other end of the scale, a less
2 impactful disease may mean that compliance with
3 contraception is no different from the general
4 population of the same age group, and, hence, justify
5 other methods to ensure patient education and
6 contraceptive compliance that may be regarded as more
7 intrusive. These variables indicate that each drug has
8 to be considered carefully and individually against its
9 particular disease setting.

10 Turning to population, the population, as a
11 whole, who may be prescribed a teratogen also have to
12 be evaluated: the age spectrum of the intended
13 population, the proportion of females of reproductive
14 potential. Then comes the potential for usage beyond
15 the indicated population. Can off-label use be
16 anticipated? If so, where may be it used and what are
17 the attendant risk possibilities? How can a product's
18 overall risk management approach be designed to ensure
19 that off-label use is adequately covered from a
20 pregnancy exposure avoidance perspective? Beyond off-
21 label use, is there the possibility for drug diversion
22 and sharing? If so, can patients be educated in the

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1 product's risk to dissuade them from sharing?

2 Then there is the need to think beyond

3 patients themselves, those in contact with the

4 patients. Is the teratogenic drug present in blood or

5 semen? Are there implications that warrant male

6 patients to be included within the REMS? Then is the

7 drug likely to be used and handled in a hospital or

8 community setting? If pregnant caregivers or health

9 care providers handle the drug, what is the risk to

10 them and how can it be addressed? Overall, the

11 intended and unintended population have to be carefully

12 evaluated on an individual drug level.

13 Turning to the benefit of the drug, it is

14 critical to appreciate the benefits of a drug, despite

15 being teratogenic, conveys to patients and the public

16 health when considering risk management. While risks

17 of drugs may be less well characterized, clinical

18 benefits of a drug in the approved indication are

19 evidenced by adequate and well-controlled

20 investigations such that we are confident the drug

21 provides both clinically meaningful and statistically

22 significant outcomes. Therefore, while there is

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1 teratogenic risk, a drug may confer survival benefits
2 in a disease, the drug may provide symptomatic relief,
3 sometimes very important to a patient's quality of
4 life. These benefits may be sustained or transient.
5 From a population standard point of view, it's
6 important to ensure that the benefits of a drug are
7 effective when considering types of risk management and
8 subsequent access to the product.

9 Then comes the probability and nature of the
10 actual teratogenic risk. Risk certainty is this next
11 variable, and it plays an important part in the
12 decision-making around optimal risk management
13 approaches; so, too, does the nature of the resulting
14 harm. New pregnancy and lactation labeling approaches
15 will hopefully do much to enable a more informed
16 decision by prescribers and patients around the risk
17 proposition of individual drugs. In the same way, the
18 probability of risk flows directly to decision-making
19 around the type and design of a risk management
20 program. A high probability of a devastating birth
21 defect or fetal death will naturally equate with the
22 most rigorous risk management approaches.

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1 Then there is the period of time in a
2 pregnancy when the risk is at its greatest. The first
3 trimester is critical for most teratogens, but not all.
4 Can these distinctions drive different approaches to
5 risk management?

6 Bringing all of these considerations back
7 together, we hope that it is apparent that specific
8 drugs carry specific and distinct risks. The benefits
9 of these drugs and they operate in different diseases
10 and different populations. As a consequence, risk
11 management strategies that balance burden and program
12 benefit will not be the same.

13 Access. By their nature, REMS programs with
14 ETASU have the potential to impact access. The more
15 stringent the controls, the greater is this potential.
16 Orphan disease drugs may translate to a greater
17 willingness to accommodate burden, while a smaller
18 discrete prescribing population may ease the targeting
19 of this program.

20 At the other end of the spectrum, prevalent
21 diseases with high rates of drug exposure and a more
22 heterogeneous population may necessitate stricter

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1 controls as a basis of permitting access. We are
2 constantly reminded that we are in the early days in
3 the advent of risk management programs and that better
4 information is needed around the impact of restrictions
5 and opportunities to bolster access amidst these
6 restrictions.

7 Safe use. The ultimate goal of any drug is
8 that it's safely used. This can be measured for
9 teratogens by how many pregnancies there were and what
10 were the outcomes of those pregnancies and what were
11 the root causes of these pregnancies, the failure modes
12 and effect analysis. Because different risk management
13 interventions are in place due to differences in
14 diseases, drugs, and drug benefits, it's important to
15 share what works and what improvements can be made.
16 However, what may work in one program with a disease
17 and drug may not be generalizable to another similar
18 program in a different population with a different
19 disease. We encourage recognition that risk management
20 operations and effective measures should not only
21 capture numbers of pregnancies and outcomes, which are
22 the failures of the program, but also to understand the

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1 true success of a program, an estimate of the prevented
2 pregnancies and birth defects could be undertaken, as
3 well as understanding if access to drugs' benefits were
4 impacted.

5 We touched on this principle of balancing
6 burden earlier in the presentation, but we would also
7 like to ensure that any discussion around burden is
8 comprehensive. Since the introduction of REMS programs
9 following 2007, a lot of discussion has been polarized
10 around the burden stemming from REMS operation, but
11 less is being discussed around the burden that might
12 otherwise stem from fetal harm. There is the impact on
13 the unborn, the impact on the patient and the patient's
14 family, the broader impact on society and the financial
15 impact to those who have to help.

16 I would hesitate to refer to this group on
17 the right-hand side of this graphic as the silent
18 minority. I would hesitate because there are many very
19 effective groups who tirelessly lobby in the interests
20 of the unborn, but it's a source of constant reminder
21 to all of us to maintain a bigger picture view as we
22 contemplate these issues.

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1 Drawing upon industry's collective experience
2 in the REMS environments, there are several lessons
3 that are being learned and that can be applied. As
4 we've suggested, core standards for labeling risk
5 management would be helpful. From these, REMS can be
6 constructed from a common starting point, but with the
7 opportunity for customization based on the factors that
8 we have outlined.

9 It's also evident that the same parties who
10 will operate within and are impacted by REMS need to be
11 fully represented in the development and implementation
12 of the program, but while these programs operate in a
13 spirit of shared responsibility, one party must take a
14 lead role, constantly coordinating, constantly
15 monitoring, constantly adjusting, and constantly
16 ensuring that the program retains effectiveness.

17 We have all come to appreciate the importance
18 of full stakeholder consultation to achieve balance and
19 understanding. This stakeholder input is beneficial
20 not only at the time of the program's development and
21 first deployment but throughout the program's
22 existence. This continuous state of stakeholder

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1 consultation would be helped by regularly sharing
2 updates on labeling and REMS effectiveness, as was said
3 earlier, to ensure ongoing appreciation that burden is
4 balanced by benefit.

5 One lesson that we haven't discussed in any
6 detail and which is slightly outside of the scope of
7 the meeting relates to adverse event reporting. Many
8 of these programs result in higher reporting rates of
9 adverse events as opposed to spontaneous adverse drug
10 reactions than in non-REMS settings, which needs to be
11 appreciated in postmarket data interpretation.

12 Finally, the uses, benefits, and risks of a
13 drug will change over time, and the risk management
14 system may need to adapt with it, so some flexibility
15 is warranted.

16 Turning to tomorrow's discussion, we would
17 like to pick up the following topics. For definitions,
18 females of childbearing potential or females of
19 reproductive potential, definitions around menopause,
20 and then for standards, standards for pregnancy
21 testing, and principles regarding discontinuation of
22 contraception when a drug is stopped, for

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1 effectiveness, REMS effectiveness determinations, and
2 then we would also like and welcome discussion around
3 criteria and decision-making on optimal risk management
4 approaches.

5 Next we observe that many drugs' teratogenic
6 potential are unknown before or during the early stages
7 of clinical development and that opportunity to start
8 REMS discussions and planning at that stage may be
9 helpful.

10 Finally, discussion around the possible
11 adoption of a teratogen symbol may help as a component
12 to risk management.

13 In conclusion, industry shares the Agency's
14 mission to promote public health through safe use of
15 teratogenic drugs and minimizing the risks of adverse
16 pregnancy outcomes. REMS is a shared responsibility
17 among all stakeholders: health care professionals,
18 patients, the Agency, and industry. There are
19 approaches that can be standardized, but there has to
20 be room for flexibility in approaches for given drug
21 benefits, teratogenic characteristics, disease, et
22 cetera. The greater the risk management controls, the

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1 increased likely impact on access to drugs' benefits
2 and risks. The burden of birth defects must be
3 considered along with the burden of risk management
4 controls on the health care system.

5 Thank you for your time and the opportunity
6 to address this forum.

7 Clarifying Questions for the Presenter

8 DR. WINTERSTEIN: Thank you. We will now
9 have clarifying questions from the committee for the
10 industry presenter. And I would like to remind
11 everyone that these are clarifying questions, and in
12 the interest of time, please try to limit yourself to
13 clarifying questions at this point. We will have time
14 for discussions later.

15 We have Dr. Fingert.

16 DR. FINGERT: Howard Fingert, Industry
17 Representative.

18 Thank you, Dr. Freeman, that was excellent.
19 If you could turn to your Slide 28, you mentioned here
20 -- I would like to know if you could clarify what you
21 mean by flexibility and standardization and if you
22 could give us some examples. I mean, for example, one

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1 that I think of is in the setting of drugs approved in
2 small indications, sometimes REMS are viewed as a way
3 to manage the uncertainty because you have low
4 exposure.

5 Could the flexibility also include an option
6 to reduce or actually stop a REMS once you do have more
7 certainty going forward, especially the high burden
8 component of the REMS? But do you have other things in
9 mind when you're talking about this flexibility that
10 you would like to elaborate on?

11 DR. FREEMAN: No, I think fundamentally the
12 key message is that one size doesn't fit all, and I
13 think, as has already been clearly articulated in
14 earlier presentations, there has to be an individual
15 and drug-specific conversation about an individual and
16 very specific intended and unintended patient
17 population. There clearly is some benefit in
18 considering standardization opportunities, but, again,
19 we have to ensure that we can adequately reflect and,
20 if necessary, deviate from those standards if the data
21 and other conditions dictate.

22 DR. WINTERSTEIN: Dr. Kashoki?

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1 DR. KASHOKI: I have a question about one of
2 the things that you stated as you were presenting Slide
3 16, and this had to do with the suggestion to increase
4 or augment the availability of information and the REMS
5 assessments about potential impact on patient access
6 and potential burden on the health care system. If
7 you're aware of any discussions and can share this, how
8 has industry discussed or is planning for a measurement
9 of burden, impact on burden and access, through its
10 REMS assessments?

11 DR. FREEMAN: I think this is part of the
12 maturing of the risk management environment. Clearly,
13 we've started out by focusing on the specific risk
14 objective and then identifying components that will
15 help to mitigate that risk, and I think as a collective
16 group, industry and the Agency, we haven't always had
17 the opportunity to adequately engage stakeholder groups
18 in that conversation, and then 2, 3 years downstream
19 the opportunities to refresh that conversation,
20 particularly with the benefit of hard data that speak
21 to the operating effectiveness of the programs, is not
22 something that on a prescribed basis that we've been

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1 able to adequately undertake.

2 DR. WINTERSTEIN: Dr. Liebmann?

3 DR. LIEBMANN: If I can follow up that
4 question for just a moment, particularly since I think
5 you mentioned that you're with Celgene, which
6 participates in two of the REMS, for lenalidomide and
7 thalidomide, and you referenced how this can be a
8 burden on industry, presumably your own corporation, in
9 setting up a REMS program. So you must have some sense
10 of what exactly that entails for your company as to
11 what is the burden.

12 DR. FREEMAN: Yes. It's a relatively easy
13 matter to look internally, but that isn't our main
14 concern. Our main concern is the impact on prescribers
15 who elect to continue with a prescription, and then, of
16 course, the prescribers who, when presented with
17 choices around products, may be channeled into a
18 setting which is perceived as being less burdensome but
19 possibly not the best product.

20 DR. LIEBMANN: So just to follow that up, I
21 mean, having been in private practice, I do know
22 exactly from the need to hire people what the burden

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1 can be, and I'm talking now purely financial burden,
2 and I would assume that you could do the same.

3 DR. FREEMAN: Yes, I think that would be
4 possible. I mean, I think through organized data
5 collection, that is something that will be possible,
6 not only in our instance but also in other instances.

7 I think one of the things that strikes me,
8 for example, is that given that many of these programs
9 involve the registration of participants, that that
10 could be taken as an opportunity to formally measure
11 what these impacts are.

12 DR. WINTERSTEIN: Dr. Morrato?

13 DR. MORRATO: I would just add those are
14 people that made it into the system that didn't get
15 burdened out, I guess.

16 DR. FREEMAN: Yes.

17 DR. MORRATO: So just to add, what are other
18 ways to get those that may have been screened or
19 potential patients that just, you know, because the
20 burden was too great or for whatever reason? But I
21 like your idea.

22 DR. WINTERSTEIN: Dr. Chambers?

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1 DR. CHAMBERS: I'm just curious in the REMS
2 effectiveness if you're suggesting that you could
3 measure on each of these endpoints how effective your
4 system is, being one of the most restrictive. Would
5 you see there any way to determine whether or not a
6 less restricted program would be as effective?

7 DR. FREEMAN: I think that's the \$10 million
8 question, and I think it would take some brave thinking
9 to move from a setting which is demonstrated as having
10 been very highly effective to move to something that's
11 less.

12 DR. WINTERSTEIN: All right. Seeing no
13 more questions, we will now proceed with the guest
14 speaker and speaker presentations. Thank you. Special
15 Presentations

16 Prescriber Perspective: Clinical Management
17 of Non-Pregnant Females of Reproductive Potential Who
18 Require Treatment with Teratogenic Drug(s)

19 DR. CHOBY: Thank you for the opportunity to
20 come and speak to you all today. I was invited by the
21 ladies of the committee, and they called the American
22 Academy of Family Physicians and asked for a speaker

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1 that would be interested in this area, and since I work
2 closely with ACOG in terms of being our AFP liaison to
3 ACOG, they called me to say, "Hey, what are you doing
4 on the 12th of December?"

5 I looked for the lightest colored ugly orange
6 slides I could find, as requested, because UT has
7 pretty loud orange and green slides at the Health
8 Sciences Center.

9 I'm a family physician. I'm going to be
10 talking to you today about reproductive-aged women and
11 medication prescribing kind of from the trenches.

12 We know that around 12 million women in
13 America are prescribed either Category D or Category X
14 medications each year, and this is despite numerous
15 warnings from the FDA in terms of what medication
16 safety is and the fact that 6 percent of these women
17 that are taking Category D and Category X medications
18 will become pregnant every year.

19 We know that the most common type of
20 contraception of women who are taking Category X
21 medicine is a continuous oral contraceptive, and for
22 all of us that prescribe continuous oral

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1 contraceptives, or birth control pills, we know the
2 devil's in the details, you basically have to take them
3 a certain way or they are not as effective. And of
4 women who are taking any kind of contraceptive device
5 or any type of contraceptive method, 40 percent of
6 women will become pregnant, and 90 percent of these
7 pregnancies are largely due to inconsistent or
8 incorrect use.

9 The National Ambulatory Medical Care Survey
10 looked at around 12,000 outpatient visits, and what
11 they found was in a primary setting, the most commonly
12 prescribed Category D and Category X medications
13 included anxiolytics, which are things like
14 benzodiazepines, anticonvulsants, antibiotics, and
15 statins, and when they looked at all people coming in
16 for visits, women age 14 to 44 years, some type of
17 these medications were prescribed in 1 in 13 visits,
18 which was a pretty eye-catching number.

19 Forty-five percent of the prescriptions for
20 Category D and Category X medications were written by
21 either family physicians or internal medicine
22 physicians, and, interestingly, contraceptive

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1 counseling was documented at less than 20 percent of
2 these visits. Now, certainly the number seems pretty
3 low and the question becomes, are we counseling people
4 and not necessarily documenting that we are, or are
5 women just not getting counseled? And interestingly,
6 women getting a Category X medication were counseled
7 about risk of that medication about at equal rates to
8 women given an A, B, or C category medication.

9 There was a survey of internists done in 2010
10 in terms of why and who should be doing preventive
11 services counseling in terms of birth control for
12 women, and 88 percent of the internists felt that it
13 was the responsibility of the primary care provider to
14 talk to female patients about family planning and
15 contraception, and 98 percent of them felt that
16 physician counseling that was given was the most
17 important information provided the patient, and the
18 second thing that they felt was important was
19 pharmacist information, and two of the three people
20 surveyed had seen a patient within the past year that
21 had been given a Category D or X medication.

22 So there is a little bit of a disconnect

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1 here. We know that women need to be on good
2 contraceptive if they're on drugs that can cause
3 problems with their pregnancy, and physicians and other
4 providers think it's important that we talk to women
5 about this, but the numbers don't show that as much,
6 and there is a disconnect that is probably
7 multifactorial.

8 And hopefully what I'll be talking about
9 today is the challenges in terms of primary care and
10 seeing the patients that we see and managing them,
11 about why and how we can do better with this. And
12 these are five of the things we'll be talking about,
13 quickly, because we have 15 minutes.

14 Okay. A day in the life of a typical family
15 doctor, we see about 25 to 30 patients in an average
16 day, and most family doctors, if we do -- and I do full
17 cradle-to-grave care, I do prenatal care, deliver
18 babies, take care of pediatrics, adolescent medicine,
19 midlife, and then geriatrics care, and I also do a
20 little bit of hospice, so we do the entire scope, and
21 do a lot of contraceptive counseling and a lot of
22 contraceptive advice in the office.

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1 So time matters. You do those numbers and
2 you say, hey, that's 15 minutes per patient, that seems
3 like plenty to talk about a lot of stuff. Well, when
4 you figure that's them checking in, the nurse putting
5 them in the room, me going in and talking to them,
6 coming out, writing prescriptions, writing referrals,
7 going back in and wrapping everything up, it kind of
8 cuts down a little bit into that 15 minutes. And the
9 internists basically, when they were asked, "What are
10 the problems that people have in terms of getting the
11 counseling done and talking about contraception?" 61
12 percent said time is a big issue.

13 Now, interestingly, several, probably 40
14 percent, of them commented on it's hard to bill for a
15 lot of the counseling that we do and it's really hard
16 to bill for some things like preconception visits, and
17 how do you code those and will you get paid for them?
18 And that does come into play somewhat. But 44 percent
19 also commented on lack of knowledge and also
20 insufficient knowledge of teratogens, which was a
21 pretty good number. Now, this did just include
22 internists, so it doesn't include everybody.

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1 Let's talk about the "unhealth" of America.
2 Anybody recognize this slide? Anybody see this movie?
3 Last Christmas -- I've got four kids under the age of
4 10, and I was home with them, and so I was like, "Let's
5 find something fun to do," and they said, "We want to
6 watch this movie, WALL-E," and so I was sitting there
7 kind of watching out of the corner of my eye, and they
8 had these people and they were so heavy, they floated
9 around on these like floating La-Z-Boys with the
10 television screen in front of their face and a cup of
11 cupcake mix, and that was what they liked to drink. And
12 my kids thought it was hysterical, and what concerned
13 me is I thought, oh, my gosh, it was kind of
14 frighteningly prophetic.

15 So when we look at chronic diseases in women
16 of reproductive age, the women that I'm seeing now are
17 sicker than the women I was seeing 15 years ago when I
18 was in residency training. Depression, hypertension,
19 and diabetes are all going up in terms of the incidence
20 of people we take care of. And in addition, when you
21 look at chronic disease risk behaviors, we could all be
22 healthier. Women aren't getting enough physical

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1 activity, obesity and smoking, as well as high
2 cholesterol, and the numbers of women with prediabetes
3 that I see on a daily basis are way higher than they
4 were even 10 years ago.

5 So when we look at the chronic disease
6 demographics, we see a definite difference between
7 different racial and socioeconomic groups, with our
8 lower socioeconomic groups being more heavily impacted
9 by some of these illnesses. And when you look at the
10 chronic and projected burden of these diseases in the
11 United States over the next 15 to 20 years, it is going
12 to make it very challenging to pay to take care of
13 everybody. So we are taking care of a different
14 patient population than we were 15 or 20 years ago, and
15 people unfortunately seem to be a little sicker.

16 So it's complicated. When I look at the
17 average visit that I do, family doctors will address
18 about three separate problems with each 15-minute
19 visit, and in about 40 percent of the encounters,
20 you're going to see more than three problems, and the
21 more medical conditions that you need to discuss,
22 obviously, what goes out the window? Health

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1 maintenance goes out the window.

2 When I precept my residents and they tell me
3 about the patient's five or six medical conditions and
4 I say, "Have they had a Pap smear or a mammogram or a
5 colonoscopy?" sometimes it's like, "I don't have time
6 to talk about that at this visit," and I say, "Okay,
7 you need to talk about it or bring them back."

8 So it came to mind when they invited me to
9 present at this, I started thinking about the patients
10 that I saw on an average week that would fit into this
11 group, and I had a 30-year-old lady who walked in that
12 I figured would be a really healthy and easy visit, she
13 has a strong family history of heart disease, very high
14 cholesterol, elevated BMI, smoked, she tried niacin
15 before, she tried diet and exercise, and she had an
16 elevated hemoglobin A1C. Well, I wanted to put her on
17 a statin, brought her back for a visit so I could
18 counsel her in terms of what the risks and benefits of
19 that were, and despite the fact of all the counseling,
20 she still opted for a birth control pill, and so now
21 you hope that she takes it and worry about that.

22 As far as continuity of care, the sicker our

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1 patients are, the more subspecialists that they see,
2 and we know that the more consultants that I send my
3 patients to see, the more people are writing them
4 prescriptions, and the more prescriptions they're
5 writing, the more communication plays into things, and
6 if there is a lack of communication, that really
7 increases risk.

8 So if you're managing one patient that sees
9 five or six other doctors, the chances of them being
10 put on something that's teratogenic go up a bit, which
11 brings me to the other patient that I saw a couple days
12 later, a nice 28-year-old who had had her fourth child.
13 She was obese, had chronic hypertension. When she got
14 discharged from the hospital she was started on an ACE
15 inhibitor and told to show up at the office for a Depo-
16 Provera shot a couple days later. Basically, she never
17 came in for that and came in later, was still on her
18 ACE inhibitor. She wasn't real concerned because she
19 had only had sex two or three times in that past 2
20 months. I was a little worried. Okay.

21 So my good question that I like to ask all of
22 my patients who are female and of reproductive age is,

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1 "Are you planning on having a baby in the next year?"
2 and when they look at me and say, "Uh-uh," my next
3 question is, "What kind of birth control are you on?"
4 and I usually get a, "Nothing," and so it takes me
5 right back to my original question, "So you're planning
6 on having a baby."

7 And when people still don't understand that,
8 I say, "Okay, look, you take 100 healthy women, you
9 send them all out to have sex for a year, 85 are going
10 to be pregnant by the end of that year." That usually
11 gets their attention and they're saying, "Hey, what can
12 I get on to prevent this?" Okay.

13 Yeah, and that's the patient with the big old
14 question mark. Okay. I'm going to keep pushing my
15 clicker until my slide advances. You never have one
16 good talk without an audio-visual glitch here, you all.
17 Okay. There we go.

18 Another thing that really plays a role in
19 primary care, controlled substances, used to be that we
20 would just worry about women taking street drugs, but
21 what I worry more about are women, the numbers of
22 women, coming in on controlled substances, who are

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1 getting benzodiazepines, OxyContin, chronic opioids
2 from either other providers or even off the street, and
3 we know that the numbers of pain killers sold in the
4 U.S. has gone up substantially, and lethal overdoses as
5 well, and being a family doctor who manages not only
6 the prenatal care aspect of things but also takes care
7 of some of these children afterwards, we're seeing a
8 lot more babies that are requiring detoxification as
9 infants, and this is something that we need to keep in
10 mind.

11 So some food for thought. Hopefully I'm
12 staying on time.

13 And when I talk to my residents, I always
14 tell them that women who are over 30 and over 40 and
15 over 50, they still have sex, and they also can get
16 pregnant, and you don't want to be the one telling the
17 lady, "Oh, by the way, the pregnancy test is positive,
18 and we might have talked about this before."

19 We've gone to pain as the fifth vital sign,
20 you know, "What is your pain? How is your pain doing
21 today?" as a way to gauge how people are suffering in
22 terms of chronic pain. Maybe we could think about the

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1 last menstrual period as the sixth vital sign and just
2 ask, it takes 2 seconds to say, "Hey, when was your
3 last period? Was it normal? Was it not normal?"

4 And from having personal experience with
5 this, I went to see my family doctor, and I was like
6 sneakily about 4 months pregnant and she didn't know,
7 so I gave her my last menstrual period, and she didn't
8 really ask me until I said -- she wanted to prescribe
9 me something, and I said, "Hey, look at that period,"
10 and she just looked at me. It probably wasn't real
11 nice, was it?

12 (Laughter.)

13 DR. CHOBY: But, you know, if you don't ask,
14 you don't know.

15 And then impromptu preconception counseling.
16 You may not get paid for that preconception visit, but,
17 shoot, if I have you in my office and I can basically
18 say, "Are you wanting to get pregnant in a year?" and
19 if they say, "No," I'll say, "Okay, can you take a
20 prenatal vitamin with folate at least and come back in
21 and talk to me about other health risk modification
22 strategies we can do to get you and your partner as

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1 healthy as we can get you before you decide to have a
2 baby?" and patients really like that and they tend to
3 come back and often talk with you to be as healthy as
4 they can be before the baby.

5 And then other considerations, we're probably
6 not going to be able to change how the health care
7 system is run, how we're compensated, how much time we
8 have to see a patient, but electronic health records,
9 you can program in prompts that you like, you can
10 program in a prompt for, "When was your last menstrual
11 period?" you can program a prompt in for, "What kind of
12 contraception are you on?" We can continue to educate
13 medical students, residents, and practicing physicians
14 about contraception.

15 One of the studies that we looked at in terms
16 of it surveyed four or five different areas of the
17 United States, family doctors and internists, about
18 just asking them what they thought the failure rates on
19 regular contraceptive methods available were, and
20 education is interesting. What they found is for
21 family doctors, at least those of us that do a lot of
22 prenatal care and do a lot of women's health, we know

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1 the numbers, but I think everybody can know them if
2 they're exposed, and working women for well woman exams
3 or preconception visits at other opportunities.

4 Up-to-date resources at the source of care
5 are wonderful if there is one place that people can go
6 get quick information that's readily accessible and
7 understandable by most of our patients because many of
8 my patients read on about an 8th grade level. We need
9 to make sure that we can get people the information.
10 And also pharmacy prompts.

11 So that is what I have, and we will turn it
12 over to the next speaker.

13 Prescriber Perspective: Clinical Management
14 of Pregnant Females Requiring Treatment with
15 Teratogenic Drug(s)

16 DR. WISNER: Thank you so much for the
17 invitation to speak with you today. I come with the
18 perspective of being a perinatal psychiatrist, so a
19 psychiatrist who treats primarily obstetrical patients,
20 and I've written thousands of prescriptions for
21 pregnant women through my career. So again that's the
22 perspective.

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1 One of the things that we've been talking
2 about a lot is risks of medication for use in
3 pregnancy, and I wanted to put this slide up to
4 emphasize the disease burdens that we're treating
5 because so often we get focused on the risks of the
6 drug but not the risks of the disease. And so this is
7 a poem that a patient gave me, and I'll just call your
8 attention to the last stanza. "You say I'm carrying
9 life inside. How can that really be? How could life
10 possibly survive in a nonexistent me?" So this is a
11 patient who had bipolar disorder with severe mood
12 disturbance. Mood disturbances are not only in the
13 brain, they're whole-body, physiologic dysregulation
14 illnesses that carry a risk for suicide, and these are
15 important burdens that I'll emphasize throughout this
16 talk.

17 So for the illnesses that I see -- and Dr.
18 Choby also mentioned how common depression is in
19 childbearing-aged women. These are epidemiologic data,
20 and I kind of pull at my epidemiologic injustice slide
21 because the risk for depression, as you can see, goes
22 up in females and continues across the lifecycle until

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1 the end of childbearing years, there is a
2 perimenopausal blip, and then it comes down, and the
3 risk for depression in women is twice that of men, and
4 the peak is right during the time when women are
5 bearing children where the injustice of having the
6 highest risk for major mood disorders occurs during the
7 childbearing years.

8 The other point of this slide is we're
9 talking about one out of five women experiencing a
10 major depressive episode, and one out of eight men.
11 It's a huge public health problem, and, in fact, the
12 World Health Organization identified depression as a
13 leading cause of years lost to disability.

14 So what do we know about this illness and how
15 can we frame it to fit the goals of this general
16 discussion? Well, in terms of disease burden, we do
17 know that if a woman is already being treated for
18 depression when she comes to pregnancy, finds out she's
19 pregnant and she discontinues her medication, that many
20 more women, 68 percent, will experience relapse if they
21 discontinue as opposed to 26 percent if they continue
22 medication. Now, that's a significant difference, but

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1 if you think about it, even if you continue your
2 medication, 26, 1 out of 4, will become ill in
3 pregnancy. I think the reason for that has to do with
4 pharmacology and maximizing pharmacology, and I'll talk
5 about that a little bit later.

6 The other hope was that if a woman
7 discontinued her medication, that at least she would be
8 well through the first trimester, but this study
9 indicated that that was not the case, that in fact
10 recurrences were quite rapid. So we have a disease
11 with substantial burden that recurs in women who are
12 maintained on medication or when they discontinue their
13 drug treatment.

14 So in response to the prevalence of this
15 illness, our American Psychiatric Association convened
16 a group of psychiatrists interested in this problem to
17 think through a risk-benefit decision-making process,
18 and I would like to share with you the process that I
19 go through that's elaborated a bit from our original
20 scheme, but just to give you a sense of how difficult
21 this kind of assessment is.

22 So when I see a pregnant woman with bipolar

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1 disorder, depression, sometimes they're psychotic,
2 sometimes they're suicidal, when I see her initially in
3 consultation, my first part of the evaluation has
4 nothing to do with drugs, it's a process assessment of,
5 "What is she expecting from the consultation? What can
6 she understand about risk concepts?"

7 Dr. Choby mentioned sometimes 8th grade
8 reading level. Sometimes I have women whose focus is
9 so poor that concepts have to be simplified. And if
10 you think about the kinds of concepts we're talking
11 about, looking at a series of studies with different
12 risk levels, and then coming to some conclusion about
13 the risk in general, and then transposing to, well,
14 what might be the risk for her individual situation? So
15 this part of my consultation has to do with, "Can she
16 even understand the kinds of concepts that we have been
17 talking about quite freely during this meeting so far?"

18 The other piece is a look at the decision
19 process itself in that a survey that we did recently to
20 look at, "What do patients want from the process?" What
21 they wanted, the majority said they wanted, was the
22 physician to give information in an understandable way

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1 about the risks and benefits of the medication, but
2 they wanted to maintain the decision-making around how
3 applicable it was to their particular situation and
4 their decision-making process. So, again, I probably
5 spend a fair amount of time just thinking about, "How
6 am I even going to convey information to this
7 particular patient?"

8 My approach to data collection in this
9 consultation, I start with not assuming anything. I
10 don't assume that the diagnosis they're coming to me
11 with is correct or complete, and I often find unipolar
12 depression that's misdiagnosed, and it's usually
13 bipolar disorder. I often find a number of comorbid
14 medical conditions, often hypothyroidism, anemia, and I
15 always then move to a standard look at, "What is her
16 illness experience now?" So I'm not just writing her
17 symptoms, I get a quantitative measure of her mood
18 symptoms at the time because it's crucial in following
19 her along through pregnancy to look at whether whatever
20 intervention I'm providing is doing anything to improve
21 her function and her disease burden.

22 The other parts of this, also mentioned by

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1 Dr. Choby, were the exposure to other kinds of negative
2 experiences, so smoking, alcohol, other drugs,
3 environmental exposure, and I also characterize the
4 disease exposure, so, "How much exposure to
5 hyperglycemia?" "How long and how severe has her
6 hypothyroidism been?" And then her pregnancy course to
7 date, ultrasounds, testing.

8 So this is a lot of information gathering.
9 And I think the most important thing that I teach my
10 residents is to, before you write the prescription, put
11 all of this down in the chart because if there is a
12 negative outcome, it's very easy to blame the drug --
13 "blame" is the wrong word -- to implicate the drug that
14 was prescribed as opposed to these other environmental
15 exposures that tend to be lost over the course of
16 pregnancy and are not remembered.

17 So this is a model basically from the article
18 that I spoke about, and the important aspects here are
19 the structuring of the problem which I spoke about for
20 that individual patient, likelihood of outcomes of
21 adverse events, but this could be any disease state.

22 And I really want to emphasize that the

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1 question that we all want to know is very hard to
2 answer from the literature, so the real question that
3 I'm interested in is, "What are all the risks of all
4 these negative things?" which our literature covers,
5 but, "What is the evidence that treating the disorder
6 and reducing the disease burden improves outcomes for
7 the mother and the fetus?" That's really what we want
8 to know, and that's why any of us would even sign a
9 prescription, because we believe that the impact on the
10 disease burden will have benefit for that mother and
11 infant, and yet if you look in the literature, it's
12 very difficult to find that kind of information.

13 So it's only recently that we've been looking
14 at what are the depression scores in women treated with
15 antidepressants, or more recently even, what is the
16 impact of depression or antidepressants on complex
17 outcomes in infancy, like the ability to recognize non-
18 native speech?

19 And just as another example of a benefit and
20 the way I think our field needs to go to again focus
21 not only on risks but on the benefits side, there is a
22 recent paper that shows that women who have high

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1 anxiety levels during pregnancy have infants who have
2 an abnormality in sensory gaiting. So this is just a
3 test that's done during sleep, you present a stimulus,
4 the baby's EEG goes like this, you present a stimulus
5 exactly the same, and the normal response is for that
6 stimulus to be attenuated. If it's not attenuated,
7 it's a marker potentially for attentional problems,
8 eventual mood disorders, psychosis. When that anxious
9 mother is treated with an antidepressant, the baby
10 sensor gaiting becomes normal, and these are again the
11 kinds of outcomes that we have rarely looked at,
12 documentation that the clinician can use in addition to
13 all of the risks to look at the benefits of treatment.

14 And again this slide really emphasizes what
15 we've talked about so far, that this is not a one-time
16 decision, that if a drug is prescribed, I think the
17 prescriber needs to document that the intended benefit
18 of the drug occurred and change plans if that has not
19 happened.

20 Again, to emphasize, are we really asking the
21 right questions? Again, lots of papers about risks but
22 very few papers about the benefits of drug treatment.

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1 So these next three slides are not designed
2 to give you a whole overview of a particular drug class
3 in pregnancy, although what I'm trying to show here is
4 the struggle that I have in distilling the literature
5 and presenting information to patients about specific
6 reproductive outcome domains for any drug. So you
7 certainly can't go through and say, "Dr. X found this,
8 these are the risks," because you have to choose which
9 domains you are going to provide that patient with
10 information about and help her understand what those
11 risks are related to her particular situation.

12 The longest one here is behavioral
13 teratogenicity, meaning, what kind of impacts might
14 there be on development of that fetus who was exposed?
15 And that tends to be the major concern of the patients
16 that I see, and it's also some of the more difficult
17 kinds of outcomes to describe, in part again because
18 the maternal disease states that I see definitely
19 impact infant outcome and infant development.

20 So my strong feeling is that if I decide to
21 prescribe a medication for a patient, it's again
22 because I believe that the disease burden reduction

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1 will yield a better outcome for that mother and fetus,
2 and I am intent on if a drug is prescribed, I'm going
3 to use it maximally, I am going to use it in a way that
4 reduces the disease burden to the maximum extent
5 possible. That means then systematic monitoring of
6 symptoms through pregnancy. It also means an awareness
7 of the pharmacokinetic changes during pregnancy.

8 All too often I see patients who are treated
9 with a starting dose, say, of an antidepressant,
10 they're marginally better, and because the levels of
11 antidepressant drop across pregnancy, they become ill
12 again, so they have two exposures.

13 So I think we must treat effectively and
14 optimally during pregnancy and be aware of these
15 pharmacokinetic changes that occur for many drugs, and
16 which is an evolving literature in itself. The other
17 piece of that, of course, is, how does the
18 pharmacokinetic change in pregnancy revert in the
19 postpartum period?

20 And I wanted to point out what I think is an
21 interesting thing to contemplate for this group, which
22 is the recent Surgeon General's report on

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1 breastfeeding. There is a chart at the end of that
2 report which is framed as here are the excess risks
3 that are associated with not breastfeeding your baby,
4 so the benefits of breastfeeding are, but not
5 breastfeeding your baby incurs a risk for some percent:
6 otitis media, asthma, allergies. It's a
7 different way of framing the question that I assume
8 they thought would have much more impact.

9 This was designed just to show some data from
10 our group, which is these are level-to-dose ratios, so
11 what you're seeing is the serum levels of drugs
12 dropping across pregnancy and then rebounding in the
13 postpartum period, this one for sertraline and this one
14 for another antidepressant, citalopram, same pattern,
15 the drug and metabolites decrease. So that if the
16 woman responds to a level here, at this point she is
17 going to be undermedicated. And again I think if we're
18 going to provide the drug, we need to provide the drug
19 in a way that it will work.

20 So what's a practitioner to do? What my
21 colleagues tell me is there is a lot of information out
22 there, but it's all over the place, and they want one

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1 source for information about risks, about benefits,
2 about pharmacokinetics, about impacts of the drug on
3 pregnancy itself, kind of one place to look for all of
4 this information. That's the piece for the data.

5 The second piece, and the most common call I
6 get, is help with interpreting the data for an
7 individual patient, so again that process piece that I
8 spoke about is crucially important in using the data
9 effectively to treat patients. And I commonly use the
10 Organization of Teratology Information Specialists, who
11 provide such free service in that regard to patients.

12 So this meeting is about the REMS guidances,
13 and we've heard a lot about the particular guidances
14 and the way those are managed. And I picked out a few
15 of the components of them just to speak briefly about
16 here, and one is the communication planning, so
17 providing risk information to professional societies.

18 And I've been involved in doing some of that
19 myself through APA and ACOG, and I think that that
20 tends to reach the thought leaders in the field, who
21 tend to be the people that practitioners call, but I
22 think that it's fairly limited in a couple ways. One

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1 is that it almost immediately goes out of date, so it
2 has to be updated to be particularly useful. The
3 second is that practitioners who have 15 minutes to see
4 a patient barely can remember where it was they heard
5 that information. So locating, "Gee, I heard this,"
6 and not only for drug prescribing in pregnancy, but
7 drugs in general, there has to be an easy place to go
8 to get information.

9 The other area that I feel terribly about
10 when I am working with patients is to say to a young
11 woman that the drug that she's taking that we have no
12 data. So the plan to use registries to collect data on
13 drugs released for use in childbearing-aged women I
14 think is crucial, because what happens, as we all know,
15 is case reports come out, there's a negative event,
16 everybody is worried about using the drug, but we don't
17 know the denominator, so we don't know much about its
18 particular risk in that way. So I've been delighted to
19 see an increasing number of registries.

20 And, finally, the point about special
21 training or certifications for prescribers I think may
22 decrease acceptability and accessibility of treatments,

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1 and I'll show you some data in a minute, but this is
2 not limited as a problem to the drugs with REMS. So
3 even the drugs that are Category D or even sometimes C,
4 prescribers are very reluctant, given concerns about
5 malpractice, given concerns about watching the TV shows
6 that say, "If you are taking Drug X and your baby had
7 Y, call this law firm, you deserve compensation," that
8 affects prescribers as well.

9 So even at the level of Category D or boxed
10 warnings, prescribers get very anxious. And I
11 certainly have had the experience of patients coming to
12 me saying, "Well, I'm coming to your research project
13 because my doctor said she couldn't prescribe any
14 medication for me anymore because I was pregnant, and
15 she referred me to another doctor, but there is a 6-
16 month waiting list." So an anxiety around prescribing
17 I think does impact accessibility and acceptability of
18 treatments for the medications that I prescribe and for
19 the group of patients that I see.

20 And we have a problem with this anyway in
21 America, and I wanted to show this data, which are, how
22 often do women with major mental illnesses seek

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1 treatment? And this is not only drug treatment. So
2 this is accessing mental health service, mental health
3 utilization for women who have been pregnant in the
4 last year and nonpregnant women. It's a problem in
5 general. Most patients in America are neither
6 identified nor treated for depression. However, we
7 look at non-pregnant women for all disorders, 16.5
8 percent pregnant women. It drops. Look at mood
9 disorders, the main group of women that I see, 25
10 percent of non-pregnant women, if they've been pregnant
11 in the last year, it's 14.

12 So pregnant women are a disadvantaged
13 population anyway, and there are so many factors that
14 make the legitimate and good desire to reduce the risk
15 of medication, the tension is always, "And what does
16 that mean in terms of increased burden of untreated
17 disease?" And those are difficult to quantify but
18 certainly are alive and well in the world in which I
19 practice.

20 I have looked forward with great anticipation
21 and followed the proposed rule on pregnancy and
22 lactation labeling, which I think addresses a number of

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1 these problems and provides the kind of format that
2 will be much more useful to clinicians particularly
3 with risk summaries and information about pharmacology
4 and the quality of data. So is it five case reports or
5 is it 10 large-scale studies that are providing
6 information to patients and practitioners?

7 So I'll finish with this slide, which is
8 again designed to focus on what we are all focused on,
9 which is the importance of reducing disease burden from
10 both the disease and minimizing risk from medications,
11 but again urgently focusing more on benefit to allow
12 the practitioner to bring that more comprehensively
13 into that risk-benefit equation.

14 Thank you.

15 Patient Perspective: Female Patients of
16 Reproductive Potential Experience with Teratogenic
17 Drug(s)

18 MS. RYAN: Hello. I'm going to be a little
19 unconventional and not use slides. So I'm giving the
20 patient perspective, so I just wanted to talk to you
21 all a little bit about the experiences that kind of I
22 can bring to the table.

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1 So my name is Kate Ryan. I'm with the
2 National Women's Health Network. Essentially what we
3 are is a membership-based nonprofit. So we work to
4 improve the health of all women, and the ways that we
5 do that are supporting informed decision-making in the
6 health care capacity, and we bring the voices of women
7 to you all, to policymakers, to regulatory bodies. Our
8 members include women throughout the United States, and
9 they actually support us with their donations, so we
10 don't take financial contributions from corporate
11 entities outside of foundations.

12 So the subject of this meeting, how to
13 protect against the risk of teratogens that they pose
14 to women without undermining the health of women with
15 unnecessarily restrictive rules, is critically
16 important to the women that we represent. Our members
17 understand this. Women who might become pregnant
18 understand this at their core. They're trying to live
19 healthy lives, and they want to know about access to
20 products that might undermine the health of a
21 developing pregnancy, that worries them, but they also
22 want reproductive autonomy and they want to be able to

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1 make the decision that feels right to them. We've been
2 involved with a cross-section of this since our
3 founding, and we really appreciate being involved in
4 today's discussion.

5 This isn't the first time the FDA has
6 convened an advisory committee meeting to evaluate
7 risks like this or even programs that prevent women
8 using teratogenic drugs from becoming pregnant. In
9 fact, the Network spoke over 20 years ago, obviously
10 not me, at an advisory committee meeting, in May of
11 1990 on a similar topic, and I spoke last year talking
12 about the iPLEDGE program, so you may have remembered
13 me from then, and my comments today will have a similar
14 theme, though I'll talk a little bit more about our
15 program services for our members.

16 So for the women we represent, it tends to
17 come down to access and information, that's their
18 bottom line. They don't think the FDA should limit
19 their access to an effective medication because of
20 their potential to become pregnant. At the same time,
21 women want to know that they have the information they
22 need to understand the risk of severe birth defects

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1 associated with fetal exposure, and they want
2 information about how to prevent a pregnancy, and it's
3 not just the information, it's also access to the
4 effective contraceptive methods that they need to help
5 them do that.

6 So we support the use of REMS for women's
7 safe use of these drugs mostly because we understand
8 the purpose of the REMS being that it's trying to
9 ensure access to drugs that people wouldn't otherwise
10 have access to, and we certainly don't want women who
11 might become pregnant to not have access to something
12 because of that potential.

13 Before I jump into some women's stories that
14 I'm going to talk about, I wanted to explain a little
15 about how we hear from women. So part of what we do at
16 the Network is provide an information service. We
17 provide women with information about medical options.
18 Since our founding, we have hosted a clearinghouse
19 called the Women's Health Voice, and it's essentially a
20 service that at its founding, we would receive letters
21 and we would do research in a medical library and write
22 them back letters about different health care options

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1 to them, now, obviously, women e-mail us or call us,
2 and our goal is to get them timely and accurate
3 evidence-based health information. So we don't make
4 physician referrals or give diagnostic or treatment
5 advice; rather, we just provide evidence-based
6 information on anything from uses of drugs to different
7 options of medical procedures, risks and benefits of
8 drugs, devices, procedures.

9 Essentially, we believe that with the right
10 information, all women can make good decisions about
11 their health care, and our goal is to provide women
12 with the tools they need to do that.

13 So, as I said, we're membership based, and
14 many of the women who call us are members, but the
15 Women's Health Voice is an open service, and so they're
16 certainly not all members. We hear from women across
17 the country of all ages and races about a variety of
18 health issues from, "My daughter just got her first
19 period, and how do you think I should explain that to
20 her?" to questions about hysterectomy and fibroids, to
21 questions about menopause and bisphosphonates for
22 osteoporosis. So it's a huge range of issues, we get

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1 many calls a day, and it's fully staffed all the time.

2 So the different pieces that we tend to do in
3 this capacity is they've received a treatment
4 recommendation and want to know what we know about it,
5 they want to know about options; they don't feel they
6 have that. So a lot of women do actually call about
7 drugs with risks of birth defects, and they may not
8 know what they're calling about is a provision of a
9 REMS, but they're asking about the provisions of REMS.

10 So women taking drugs with a risk of birth
11 defects and REMS requirements have contacted the
12 Women's Health Voice and have some questions and
13 concerns that I wanted to bring. Their perspectives
14 run the gamut from women who feel a strong concern
15 about a drug and feel really comforted by the
16 protection of REMS, and women who are really annoyed
17 and offended at required pregnancy testing. So I'm
18 going to share a few examples.

19 One of them is a woman in her fifties who was
20 writing, her 18-year-old daughter was prescribed
21 isotretinoin, and she was really concerned because she
22 knew it had a risk of birth defects. She wasn't at the

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1 health provider visit with her daughter, but her
2 daughter explained, "My doctor prescribed this and he
3 said I have to go on birth control and pregnancy
4 tests," and what this woman was actually concerned
5 about is that's worrisome to have birth defects, but
6 this woman was also a DES daughter, and so for her,
7 this just struck right at her heart, and so she was
8 extremely distressed, she wanted to know more about why
9 her -- you know, she thought it was great that the
10 doctor was talking to her daughter about being on
11 contraception and getting pregnancy testing but didn't
12 understand what that meant and why that was being done.
13 So we explained what the REMS was and explained all of
14 this, and she was very supportive and felt that it was
15 a protection for her daughter that she wished her
16 mother had had. So for her, that was huge.

17 At the other end of the spectrum, we had a
18 woman who called because, frankly, she found the REMS
19 provisions unnecessarily burdensome. She was a medical
20 student, so I'm sure that probably played a piece into
21 -- this is a room full of doctors -- so I think she
22 felt that taking a drug with a risk of birth defects,

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1 and it had required monthly pregnancy testing as one of
2 those REMS, and she was basically calling to express
3 her objections and asked what the heck was going on
4 because she thought it was burdensome and she thought
5 it was sexist because she was a medical student, she
6 described difficulties trying to deal with her training
7 and having to go in for these monthly tests, and she
8 was a medical student, and she was responsible enough
9 to when her doctor talked to her about, "This is your
10 drug, these are birth defect risks, these are
11 contraceptive counseling," you know, she felt she could
12 take a contraceptive, responsibly follow through with
13 that, and felt basically that her doctor or health care
14 authorities weren't trusting her to make an effective
15 decision for her health care, and essentially she
16 pointed out that she could use this responsibly, and
17 even if her contraceptives failed, she could seek an
18 abortion, and she didn't feel that it should interfere
19 with her life this much.

20 Obviously, those examples are at ends of
21 spectrum, and there are women obviously in the middle.
22 There are women who call and have questions, they find

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1 it annoying, but when we explain the purpose, they
2 understand, they get it, but they're irritated, and
3 that probably is most women that we hear from, but we
4 do hear from women at other ends of the spectrum.

5 So I also want to talk a little bit about
6 respecting women's decision-making in this context.
7 This is a sensitive subject, and what these examples
8 have in common is that women want the information, they
9 need to make an informed decision, but they want to be
10 recognized as responsible individuals who can make and
11 follow through with a health care decision that affects
12 their bodies and their health and their potential
13 pregnancy, if it came to that.

14 So one of the risk management tools -- and
15 some of this is stuff that we'll talk about tomorrow,
16 but I'm going to use my time today to cover a little
17 bit on that as well -- are the Elements to Assure Safe
18 Use, like the pregnancy testing, like the contraceptive
19 counseling. We fully support the intention of the risk
20 management strategies that are essentially trying to
21 support women who want to avoid becoming pregnant while
22 taking one of these drugs, and it's really important

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1 that their providers are being encouraged to do
2 contraceptive counseling. As Dr. Choby said, less than
3 20 percent are documenting that they're doing that, at
4 least in the family care setting, and from what we hear
5 from women, it's not just that setting, a lot of women
6 aren't getting contraceptive counseling, that when they
7 leave they feel like they know what they're talking
8 about.

9 But we also feel, in this context
10 specifically, that it's really important that her
11 choice be voluntary, that she chooses the method that
12 she wants and feels comfortable with even if it isn't
13 the most highly effective. Obviously, there is a lot
14 of talk about IUDs and long-acting contraceptives. We
15 think they're great, but if a woman doesn't want to be
16 on one, that's her decision, even in this case. If she
17 would rather use condoms rather than a hormonal method
18 for whatever reason -- and women have lots of reasons
19 they don't like being on hormonal contraceptive methods
20 -- that she should be informed about the risks, her
21 doctor should be very clear about that, but that she
22 should then also be informed about emergency

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1 contraception and legal abortion care, these are all of
2 her options, and it's important that women have the
3 autonomy to make a decision that's right for them, in
4 particular when it comes to contraceptives. So we are
5 a little concerned about some of the REMS that do
6 require a hormonal contraceptive for those reasons.

7 Another aspect of the contraceptive
8 counseling that I want to highlight are ways that
9 doctors can effectively communicate with women about
10 different contraceptive options. There are really good
11 tools out there that don't get as much use as we wish
12 they did, as we wish they would, and this is something
13 women contact the Women's Health Voice about as well,
14 so they sort of leave their doctor's office and still
15 have questions about Depo or an IUD or the difference
16 between two different pills.

17 And also, as Beth had said, this is a
18 difference between time constraints, providers maybe
19 not feeling comfortable talking about contraceptives
20 with women, so they leave and they still have
21 questions. And one of the tools that we kind of turn
22 women to when they call us is called the Birth Control

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1 Comparison Chart. So it's published by the Cedar River
2 Clinics. It's a provider group. Actually, the
3 provider group is also a member of the Network and has
4 been for about 20 years, I think, and they're based in
5 Washington State, but it's this really women-friendly
6 tool. And this is the one reason I feel I should have
7 had slides, to show this picture.

8 But essentially what it is, is it uses
9 nonmedical language, it uses pictures and colors and
10 8th grade literacy levels, and it breaks it down by
11 method, so barriers, hormonal, long-acting, and
12 sterilization, with pictures, with explanations. You
13 click on it, it gives you a lot of details that aren't
14 necessarily medical, which women don't care about, they
15 want to know what the range of effectiveness is, they
16 want to know if it would interact with anything else
17 they might be taking. Obviously, we hear from
18 information seekers, so that makes sense.

19 But what it does, which is great, the online
20 tool, is you can click on up to three different options
21 and hit "Compare," and it gives you a side-by-side
22 comparison. Women love that, and they can do it at

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1 home, and it's easy, but it's also something that a
2 provider can use to give to women, a printout, and use
3 that to talk to women during the contraceptive
4 counseling rather than spending 5 minutes explaining,
5 handing someone a chart and saying, "Look this over,
6 I'm going to touch on a few, let me know if you have
7 questions." It's a way of addressing that there are
8 very legitimate time constraints, but also most people,
9 when you just talk at them after a doctor's visit,
10 aren't in a place where they can absorb audio
11 information. I'm not an audio learner, so I get that,
12 but it's really helpful.

13 So these are the types of things that
14 especially when you are prescribing a drug that has
15 teratogenic risk to a woman who might become pregnant,
16 a really effective contraceptive counseling tool that
17 they can take home -- and in this case, a decision aid
18 -- is huge. So we really support that.

19 And one more comment before I wrap up, which
20 is about REMS in general. And this is really
21 considering REMS in context, and I sort of got at this
22 in the beginning, but the original intent of REMS being

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1 to give patients access to drugs that wouldn't
2 necessarily be approved because of these significant
3 risks, and that was the way it had been talked about a
4 couple of years ago when it was approved. And so we
5 very much support REMS in this case because under that
6 line of thinking, women wouldn't have access to these
7 effective medications without a REMS, so that's great.

8 And we understand that there are some
9 complaints, especially with the ETASU, that they can be
10 really burdensome. And we hear a lot about how they
11 can be burdensome to providers and pharmacies and the
12 health care system, and I think you all know that,
13 especially those of you who prescribe drugs that are
14 under REMS, but I think it's really important to
15 remember that it's incredibly burdensome to women. They
16 are jumping through a lot of hoops to get these
17 medications, and I think it's really important that
18 when considering any changes to these REMS, that the
19 changes be made without compromising the safety
20 standard, of course, but in a way that really is woman-
21 centered and it's thinking about the women who have
22 daily lives and maybe kids and a job and are trying to

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1 balance a lot.

2 So other things that we would recommend as
3 ways of dealing with this would be ensuring that these
4 REMS talk about other therapies that maybe could be
5 other appropriate first-line treatments. And there are
6 REMS that definitely have other medications that could
7 be used that aren't teratogenic. That's not always
8 true, there are definitely some REMS that this is the
9 only effective medication for this purpose, and in
10 those cases, if there is any overprescribing of those
11 drugs, these are things we would like to see targeted
12 because these are ways that aren't necessarily making
13 it more burdensome for women, which is the last thing
14 we want to see.

15 So just that reminder, to keep women at the
16 center when thinking about any changes that might be
17 made to these programs.

18 Thank you very much for your time, and I will
19 no longer stand between you and lunch.

20 Clarifying Questions for the Speakers

21 DR. WINTERSTEIN: We will now proceed with
22 questions. Again, let's focus on clarifying questions

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1 so that really not much stands between her and lunch.

2 (Laughter.)

3 DR. WINTERSTEIN: Dr. Wisner?

4 DR. WISNER: I thought that was just a
5 fabulous talk about the perspectives of women, and what
6 I kept thinking about this, and I wonder if I could get
7 some clarification, about whether the point that the
8 medical student was raising had to do with an ethical
9 question about, whose risk is it really? Because she
10 seemed to imply that it's her risk and she resented
11 that there were other folks trying to control her
12 control of that level of risk. So do women present
13 this as kind of a greater ethical question? Is that
14 what --

15 MS. RYAN: I think she was. This woman in
16 particular was kind of right at the otherwise healthy,
17 she had stated she was not trying to get pregnant
18 anyway, she's in med school, and she, I think, very
19 much felt that this was a level of, not quite
20 regulation, but essentially a level of kind of
21 regulating her personal medical decision-making and the
22 medical decision-making between her and her doctor

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1 because the truth is what she had pointed out, the REMS
2 she was under had monthly required pregnancy testing,
3 and that wasn't coming from her provider, so she had
4 raised just in this phone conversation with one of our
5 Women's Health Voice staffers that this is right in the
6 middle of her and her provider, she knew her provider,
7 she was comfortable with her provider, and feeling like
8 the idea that somebody else, somebody up here, was
9 between her and her provider deciding what would make
10 the most sense for her, and she did raise that sort of
11 outside the context of this is burdensome and busy to
12 me, it feels sexist because obviously only women taking
13 this drug -- and it wasn't a drug obviously only for
14 women that she was taking -- have to go through this.
15 And then, of course, the fact that the decision-making
16 was removed, not just from her, but also from her
17 provider.

18 And I think, as I understand the conversation
19 -- I didn't take this call -- she had expressed
20 thinking it was her provider and her provider said,
21 "You're going to have to do this," her response to her
22 provider was, "Are you kidding me? What are you

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1 talking about?" and the provider explaining to her, "I
2 hear you, but this is what it is to be taking this
3 drug. I'm not doing this for you personally and I'm
4 not doing this personally as a provider. This is what
5 any provider has to do for any woman on this drug." And
6 she seemed very surprised at that level.

7 DR. WINTERSTEIN: Dr. DiGiovanna?

8 DR. DIGIOVANNA: You have described a number
9 of burdens associated with the sort of a program that I
10 don't think have appeared in much of the documentation,
11 and I wonder whether your organization or whether
12 you're aware if this type of quality of life assessment
13 or these types of burdens have been identified in some
14 way. So the patients' perspective and their real life
15 experiences and how that affects their ability to go
16 forward with treatment can somehow be incorporated as
17 the framework goes forward so these various issues can
18 be identified and then attempt to be quantified.

19 MS. RYAN: I think that would be great
20 because essentially what we hear is just anecdotal
21 evidence from the women who self-select into calling
22 us. So we don't have an idea of how many women feel

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1 like this or feel that it really interferes. I think
2 it's, I'm sure, higher than we're hearing because I
3 would imagine any number of women who feel burdened who
4 don't want to take the time to call us -- our members
5 know we're here, so they're more likely to call us
6 because they interact with us regularly, but often --
7 and one of these women was not -- the woman who was the
8 DES daughter was not a member, so she had sort of
9 Googled, "Who do I ask questions?" and we pop up as
10 sort of a health clearinghouse on Google when you type
11 in "health questions" or some number of other things
12 like that.

13 But I would love to see a better sense from
14 both sponsors and from the FDA of how to measure how
15 this impacts women and not just their access but also -
16 - because access is a little different, access is
17 looking at whether or not they picked up the drug or
18 took a pregnancy test or fell outside the window of the
19 pregnancy test range in some of these REMS as opposed
20 to how much they feel like they wish they could be
21 taking another drug if that was possible. In some
22 cases, it is possible, and that's a conversation, when

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1 we can tell women that there are alternatives to what
2 they're taking, but that's slightly different.

3 DR. WINTERSTEIN: Dr. Shapiro?

4 DR. SHAPIRO: I think this is all really
5 important for us as we continue to talk about it, and I
6 will add a little bit to my earlier comment about
7 access. It's the classic clash between autonomy and
8 beneficence and beneficence now to the unborn and maybe
9 to the public, but I think that access is also related
10 because I guess one could say her choice is to simply
11 go away and she won't be subjected to the kind of
12 restrictions on what she can do or how she has to do,
13 but she can just then not have access, and that's not
14 an ideal answer either. So I think, and, again, just
15 analogously, in case law about, "Does the pregnant
16 woman have to have the C-section or not?" the answer
17 from the D.C. Court of Appeals, which is a well-renown
18 case in court, is no, that she cannot be made to do
19 something for the good of her fetus.

20 MS. RYAN: Yep.

21 DR. SHAPIRO: So I think that the lesson for
22 us, or maybe the admonition that I hope we'll keep in

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1 mind as we go through the meeting, is that to the
2 extent that we can get better data to quantify the risk
3 better, we will be more justified in imposing
4 restrictions on autonomy on her and everybody else, and
5 I think that's really an important ethical issue.

6 MS. RYAN: Yeah.

7 DR. WINTERSTEIN: Dr. Polifka.

8 DR. POLIFKA: I've heard a lot this morning
9 about the impact of labeling and REMS on physicians and
10 industry and patients in terms of costs and time and
11 access, but I haven't really heard anything about the
12 impact of labeling and REMS on women's decision-making
13 when they have an inadvertent pregnancy. So if the
14 contraceptive fails and the drug that they happen to be
15 on has a pregnancy label X or a REMS, are they, from
16 your experience, Kate or Kathy, are they more inclined
17 to terminate that pregnancy out of fear even though we
18 may not have a lot of human data to really justify that
19 this pregnancy may be affected or have an abnormality?

20 DR. WISNER: So, I'm sorry, Janine, the
21 question is, are they more likely to terminate the
22 pregnancy?

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1 DR. POLIFKA: Yeah. Do you feel that the
2 presence of a label or the REMS increases fear in
3 couples or a pregnant woman that her pregnancy for sure
4 will be affected, and so therefore they're more
5 inclined to terminate the pregnancy?

6 DR. WISNER: Yeah, I see. So I'm answering
7 based on clinical experience and not so much data, so
8 if somebody else has data -- so I see a lot of women
9 who are on anticonvulsants, including valproic acid and
10 carbamazepine, who become pregnant, and my overall
11 experience is that it is not those specific, the REMS,
12 that would lead them to decision-making, it really is
13 at a different level, it's the explanation of the risks
14 and the various domains in that process way that I
15 spoke about.

16 I actually see fairly few terminations in the
17 group that I work with, but what they tend to then want
18 to do is embrace anything that would improve the
19 outcome, so other kinds of health interventions,
20 monitoring to get the maximum benefit for the disease,
21 those kinds of things are still relevant.

22 But my clinical experience is, no, it isn't

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1 the particular category or REMS, it really has to do
2 much more with those individual specific factors, about
3 understanding the level of risk of the drug versus the
4 level of risk of the disease, and I think, again,
5 that's crucial, because some women exposed to these
6 medications -- and I'll give you an example. I have a
7 patient who every time she's off of her particular
8 group of medications, she hallucinates and has already
9 jumped out through windows, so the risk -- you can
10 always put together a level of risk for some patients
11 where anybody would say, geez, she absolutely has to
12 say on the meds. So it's those kinds of issues that
13 are more impactful I think than the labeling itself.

14 MS. RYAN: I can also say I think there is a
15 little bit of -- it's sort of hard to parse out because
16 when we're talking about being on these drugs, most of
17 these then are unintended pregnancies, and it's
18 actually quite difficult to parse out that they may
19 have sought abortion care anyway, having nothing to do
20 with the teratogenic risks, because it's an unintended
21 pregnancy, and while it's not often talked about, but
22 in medical settings, obviously a fair number of women

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1 who have unintended pregnancies seek out abortion care.

2 And so it's actually really difficult, I
3 think, to parse out, and my guess -- and I'm also not
4 speaking data, just women we speak with, but if they
5 wanted the pregnancy, they may keep it and do the best
6 they can to be healthy for the rest of their pregnancy,
7 and if it was unintended and unwanted, they're going to
8 make the decision they would have made anyway. We
9 haven't seen it play that big of a piece.

10 DR. WINTERSTEIN: Okay. Dr. Morrato, I
11 think?

12 DR. MORRATO: Yeah. Thank you. This was a
13 question for Ms. Ryan. I was just wondering if you had
14 any information that might speak to sort of perceived
15 burden among women depending on the duration of the
16 risk management, so for a drug that's used maybe for a
17 more acute short-term care versus chronic, could be for
18 lifetime care.

19 MS. RYAN: And actually I think that makes a
20 big difference with -- one of the REMS, for example,
21 was the isotretinoin, Accutane, REMS, which most people
22 aren't on for more than I think it's 6 months usually.

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1 While very annoyed, that's seen as a doable, I guess,
2 as most women can see, and they feel, "I'll remember to
3 take my pill the same time every day for 6 months, I
4 can do that," and I think it weighs differently.

5 I would also say that I think for some of the
6 REMS that have these requirements that could be used
7 for chronic use, that's when we get questions that are
8 more based on alternatives. "Is there anything else I
9 can be taking for hypertension or whatever it may be
10 that wouldn't have a teratogenic risk?" So if there is
11 not an end date, they tend to ask a lot more about
12 alternatives.

13 DR. WINTERSTEIN: All right. We will now
14 break for lunch. We will reconvene again in this room
15 in 1 hour, almost 1 hour, a little bit less than 1
16 hour, at 1:15. Please take any personal belongings you
17 may want with you at this time. Panel members, please
18 remember that there should be no discussion of the
19 meeting during lunch amongst yourselves or with any
20 members of the audience. Thank you.

21 (Lunch break from 12:26 p.m. to 1:17 p.m.)

22 DR. WINTERSTEIN: For the record, Dr. Suarez-

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1 Almazor had to leave, and she will not be able to
2 participate for the remainder of the meeting. Open
3 Public Hearing

4 DR. WINTERSTEIN: Both the Food and Drug
5 Administration and the public believe in a transparent
6 process for information gathering and decision-making.
7 To ensure such transparency at the Open Public Hearing
8 Session of the advisory committee meeting, FDA believes
9 that it is important to understand the context of an
10 individual's presentation. For this reason, FDA
11 encourages you, the Open Public Hearing speaker, at the
12 beginning of your written or oral statement, to advise
13 the committee of any financial relationship that you
14 may have with the sponsor, its product, and, if known,
15 its direct competitors. For example, this financial
16 information may include the sponsor's payment of your
17 travel, lodging, or other expenses in connection with
18 your attendance at the meeting.

19 Likewise, FDA encourages you, at the
20 beginning of your statement, to advise the committee if
21 you do not have any such financial relationships. If
22 you choose not to address this issue of financial

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1 relationships at the beginning of your statement, it
2 will not preclude you from speaking.

3 The FDA and this committee place great
4 importance in the Open Public Hearing process. The
5 insights and comments provided can help the Agency and
6 this committee in their consideration of the issues
7 before them. That said, in many instances and for many
8 topics, there will be a variety of opinions. One of
9 our goals today is for the Open Public Hearing to be
10 conducted in a fair and open way where every
11 participant is listened to carefully and treated with
12 dignity, courtesy, and respect. Therefore, please
13 speak only when recognized by the Chair. Thank you for
14 your cooperation.

15 A timing system is in use today for the Open
16 Public Hearing. The light on the timer will be green
17 when you begin your talk. When 30 seconds are
18 remaining the light will turn yellow. The light will
19 turn red when your speaking time has expired and the
20 microphone will cease to work. Each speaker has been
21 allotted time to speak and will be timed accordingly.

22 I would like to call Speaker Number 1.

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1 MS. BENEGBI: I'm sorry. I have a little bit
2 difficulty to stand up, so I will do my best.

3 Good afternoon, ladies and gentlemen. My
4 name is Mercedes Benegbi. I am the Executive Director
5 of the Thalidomide Victims Association of Canada. I am
6 also a survivor of the thalidomide tragedy. Since
7 Richardson-Merrell is the company that distributed
8 thalidomide in Canada in the late '50s and early '60s,
9 I consider myself, along with my fellow TVAC members,
10 as an American and Canadian victim of this tragedy,
11 which forever changed the use and marketing of
12 medication. I therefore feel very much in my rightful
13 place among you today.

14 I will continue by asking you not to look
15 upon me as an adversary in your debate but rather as a
16 partner who takes to heart the respect for human
17 dignity to the highest possible quality of treatments
18 to be provided to all the wide diversity of patients as
19 well as the ultimate protection of human beings yet to
20 be born because, sincerely, who would wish to be
21 stricken by a devastating or incurable disease such as
22 cancer, and who would wish to be born with a body

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1 mutilated by teratogenic drugs?

2 The reasonable burden of teratogenic drug
3 distribution programs. To give just one example, in
4 1998, the S.T.E.P.S program was declared to be the
5 safest controlled distribution program to the extent
6 possible and was judged to be indispensable by the FDA
7 if Celgene wished to market the notorious teratogen,
8 thalidomide, in the U.S.A. Despite some changes along
9 the way, this program is generally considered a success
10 since in spite of the distribution of hundreds of
11 thousands of tablets, so far there have been very few
12 fetal exposure and no child has been born with
13 resulting deformities. Of course, a rigorous program
14 requires that certain necessary steps be followed
15 because this is what guarantees its success.

16 In an era when everything has to be rushed
17 ahead at top speed and our specialists are overloaded
18 with work, all the more reason to keep in place all the
19 measures, steps, and procedure for prescription in
20 order to avoid any judgment ever or any shift toward
21 convenience that would endanger a methodology that was
22 created and developed specifically to protect your

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1 future generations.

2 In order to persuade you that these steps are
3 justified, perhaps it would have been appropriate for
4 me to give you a presentation on the three generations
5 of thalidomide victims in Brazil or simply to invite
6 you to take an excursion to Cologne, Germany, where
7 conventions of thalidomide survivor are regularly held.
8 After all, there are only a few thousand of them in
9 that country.

10 Always remember that all the health care
11 professionals, prescriber, and parents involved in our
12 concern with the birth of deformed children resulting
13 from teratogenic drugs have had a very hard time
14 surviving such a tragedy, not to speak of the
15 unfortunate number of suicides that have occasionally
16 followed.

17 During our event commemorating the 50th
18 anniversary of the thalidomide tragedy in Canada, which
19 took place this past October in Ottawa, I asked a
20 patient suffering from multiple myeloma to come and
21 give us a testimonial of her experience with
22 thalidomide. In spite of the courage on either end

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1 that was necessary to take this step, it was not long
2 before an unshakable bond of sympathy could be felt
3 between us, the survivor of the past, and her, who
4 represented the hope of the survivors of the future, to
5 understand that neither she nor we wished this fate
6 upon ourselves and that REMS programs are one of the
7 least of so many burdens of life. This unique moment
8 in the history of the use of teratogen, in itself, was
9 more than all of the bureaucratic corporate and
10 institutional debates on this subject.

11 In my opinion, nothing justifies a treatment
12 situation that is so complex and cumbersome resulting
13 from a large number of disconnected program. The
14 authorities concerned must facilitate the work of
15 oncologists and provide them with one clear and
16 effective tool for the prescribing of teratogenic
17 substance as well as the necessary and appropriate
18 education concerning their use, for their patients.
19 Furthermore, there is no justification for abortion to
20 be perceived as an easy solution in the event of
21 potential fetal exposure since, despite the many
22 challenges to be faced, I would ask you to keep in mind

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1 that the vast majority of the members of my
2 organization are glad to be alive, just as I am among
3 you here today. True, the list of --

4 (Microphone cuts off at end of allotted
5 time.)

6 DR. WINTERSTEIN: Thank you. Speaker Number
7 2, please.

8 MR. NADGLOWSKI: Good afternoon. My name is
9 Joe Nadglowski. I am President and CEO of the Obesity
10 Action Coalition. I have no personal financial
11 disclosures. The Obesity Action Coalition is a 40,000-
12 plus member organization made up of people who struggle
13 with their weight. About 93 percent of our members
14 have self-identified as being affected by obesity. The
15 remainder are health care professionals who care for
16 them. And we have about 25 companies who are members
17 as well, including both obesity drug and device
18 companies.

19 You know, the past 12 months have been pretty
20 exciting in the obesity space where we have seen two
21 new medications approved for the treatment of obesity,
22 the first of which is now on the market and actually

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1 was approved with a REMS with assurances for safe use,
2 and that drug is called Qsymia. It is a drug that is a
3 combination of phentermine and topiramate, low doses of
4 phentermine and topiramate. The REMS for that program
5 include, obviously, a medication guide, some education
6 to physicians, but there is an assurance for safe use
7 with a certified pharmacy system. However, the
8 certified pharmacy system is mail-order only.

9 And actually I stood in this very room
10 advocating for approval of this medication, urging
11 actually a REMS that was even stronger than that, and
12 I'm here today to say that, you know what? What I
13 suggested and what we've developed may not be quite
14 working in the way we thought it would. I'm not so
15 convinced that it is actually assuring safe use, and it
16 actually may be encouraging more unsafe use, and so I
17 wanted to talk to you about that.

18 Both phentermine and topiramate, the two
19 components in Qsymia, are available generically.
20 Topiramate obviously is the medication that we have
21 concerns about for today's subject. It is available
22 without a REMS across this country for other uses,

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1 including a treatment of epilepsy and migraine
2 prophylaxis.

3 So what we find is that because the process
4 in the physician's office is relatively complicated
5 where a physician has to fax in to one of these mail-
6 order pharmacies that they have to track down -- there
7 aren't a lot of them -- it's actually easier for them
8 to write the generics than avoiding the fact that we
9 have a REMS that requires education, et cetera. So the
10 system itself is actually encouraging misuse.

11 We also see, of course, that since patients
12 do have to go through this rather elaborate process to
13 achieve getting the drug at home, many bypass actually
14 doing so. They don't engage in the treatment of their
15 obesity, and, of course, we know obesity itself leads
16 to birth defects in many cases, or in some cases can be
17 considered a teratogen.

18 So I think we have to take a close look as
19 you think about these topics today and tomorrow, are we
20 designing systems that are actually encouraging the
21 safe use of these medications? Even though I advocated
22 for the system that exists now, and the certified

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1 pharmacies and the mail-order, I realize now in seeing
2 these first couple months that it is actually, in my
3 opinion, having the opposite effect, that we are
4 actually going to see more babies exposed because of
5 this issue. So I would ask you to take that into
6 consideration these next couple days.

7 Obesity drugs are going to be used by a large
8 percentage of the population moving forward. So many
9 of us are affected by our weight. They've helped so
10 many of us, myself included; however, they do have to
11 be delivered safely, and there are mechanisms to do so.
12 I still think a REMS is necessary, but the way we're
13 doing it now, where we require a certified pharmacy to
14 deliver the medication without having the generic
15 components with the same kind of certification seems to
16 me to be very flawed.

17 Thank you very much.

18 DR. WINTERSTEIN: Thank you. Speaker Number
19 3?

20 MS. FRANCE DE BRAVO: I don't know if you
21 have my name. Oh, yeah, great. I'm Brandel France de
22 Bravo, and I am pleased to have the opportunity to

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1 speak on behalf of the National Research Center for
2 Women and Families. Our Center does not accept funding
3 from manufacturers of medical products, and I have no
4 conflicts of interest.

5 Our nonprofit center analyzes and reviews
6 research on medical issues and provides objective and
7 understandable information to patients and providers.
8 We are an active member of the Alliance for a Stronger
9 FDA, which is a nonprofit coalition of corporations and
10 nonprofit organizations that has successfully increased
11 resources for the FDA.

12 I have a master's in public health, and I
13 have just reviewed the documents, I listened to the
14 presentations this morning, and I just want to provide
15 a little bit of feedback on the questions that the FDA
16 gave us to guide our thinking today and tomorrow.

17 So for Question Number 1, in my opinion, the
18 framework adequately reflects the range of factors
19 intrinsic and extrinsic, that must be considered when
20 developing a risk management strategy for a teratogenic
21 drug, but, of course, a framework is just that. As
22 we've heard, there are obviously problems that arise

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1 and it's really just a tool to guide our thinking, and
2 each drug with teratogenic risk is going to have to be
3 scrutinized on an individual basis, looking at issues
4 like the one that was just raised. Are the components
5 of this drug available to the public in other ways that
6 do not require a REMS, for instance?

7 And as the framework makes abundantly clear
8 on page 34 and again in Slide 28 of Dr. Vega's
9 presentation this morning, a factor such as the size of
10 the patient population, whether it's large or it's
11 small, can either favor a REMS or militate against it.
12 So it is pretty complicated, and as the FDA says, it's
13 highly context dependent.

14 But while reading through all the materials
15 and listening to everything, it seemed like two factors
16 jumped out at me as key, which is one of the questions,
17 "What are the key factors in determining when labeling
18 is insufficient and when REMS is called for?" Some of
19 this may just seem obvious, but I just want to give my
20 impressions. Number one is if the drug is used to
21 treat a chronic condition and will therefore require
22 long-term use, obviously that seemed important; two,

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1 the drug's potential for off-label use, particularly in
2 light of the recent court case ruling that off-label
3 drug marketing is free speech.

4 So those are the things that for me jumped
5 out as very important factors. I thought that the
6 definition of females of reproductive potential, or
7 FRPs, was adequate.

8 I think one of the thornier issues is with
9 regards to women -- this is Question Number 3 -- women
10 who are partners of male patients taking teratogenic
11 drugs, I kind of felt like we're never going to be able
12 to protect them as much as many of us would like. It
13 seems to me that REMS need to address the special risk
14 of men who are taking teratogenic drugs who are not
15 married or not in a long-term relationship and who,
16 therefore, may have multiple partners. So again this
17 just speaks to how the male patients are counseled.

18 Question Number 4, there may be instances
19 where a REMS program could or should be targeted to a
20 specific at-risk population. That said, the drawback
21 of a more targeted program is that other females of
22 reproductive potential who are also taking the drug

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1 could conceivably fall through the cracks and be
2 harmed.

3 Now, in reading the FDA's summary or
4 synthesis document, the FDA stated they couldn't find
5 documentation of patient access problems or evidence of
6 system burden due to REMS. That, of course, doesn't
7 mean they aren't out there, but we haven't had a good
8 way of documenting them. But, nevertheless, I would
9 say a strategy to mitigate the risks should address as
10 much of the at-risk population as possible.

11 Question 5, "Should REMS for a particular
12 drug vary by indication?" This is really again another
13 thorny one, and I feel that the length of drug use --
14 you know, is it for an acute condition or a chronic
15 condition? And again its potential for off-label use,
16 to me those seemed more important than the actual
17 indication.

18 So if for one indication the drug will be
19 used for a very short time, then perhaps the risk
20 management approach could vary, that's conceivable.
21 Generally, I think there is more risk to patients and
22 possibly more burden to the health care system if a

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1 drug has multiple REMS, it just makes implementation
2 that much more complicated.

3 And I just had a few closing comments that
4 are sort of separate from the framework itself and just
5 responding to some of the very interesting things that
6 we heard earlier today.

7 I thought Mr. Freeman's suggestion this
8 morning that there be a graphic or symbol for
9 teratogenic drugs, if that doesn't exist, that seems
10 like a pretty important thing that should be on the
11 label and on all counseling materials. We're dealing
12 with a lot of low health literacy and low literacy in
13 general, so we're going to need that, just as
14 cigarettes have done.

15 And again speaking to that low health
16 literacy, and also the limited time that providers have
17 and the fragmented system and all the missed
18 opportunities, it seems to me that the REMS system
19 needs to tap into new technologies, new systems of
20 health communication, including online videos and an
21 app for mobile devices, which are being used by all
22 types of populations, maybe an app for each drug.

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1 And then I thought Kate Ryan's points, of
2 course, were very well taken, and it seems like we
3 really need -- that all drugs with REMS need a very
4 good low literacy, graphic-heavy patient decision tool
5 for contraceptive use. If that doesn't exist, it
6 really needs to exist and needs to be readily
7 available.

8 So those are my comments. And I'm really
9 thankful, grateful, that you allowed me to share them
10 today. And I look forward to more enriching
11 discussion. Thank you.

12 DR. WINTERSTEIN: Thank you. The Open Public
13 Hearing portion of this meeting has now concluded and
14 we will no longer take comments from the audience.
15 Questions to the Committee/Committee Discussion

16 DR. WINTERSTEIN: We will now begin the panel
17 discussion portion of the meeting. Although this
18 portion is open to public observers, public attendees
19 may not participate except at the specific request of
20 the panel.

21 Now, I had to put myself into a framework of
22 what it is that we are actually supposed to accomplish

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1 today, and since we are not voting, it feels like it's
2 an open discussion and everybody can just voice
3 whatever they are thinking, but I would like to try for
4 all of us to come up with some tangible take-home for
5 the FDA because I think the expectation is really that
6 we are trying to provide answers, and we might conclude
7 that it be easy, and I agree on that, but let's try to
8 focus on the questions at hand and how we can come up
9 with some recommendations essentially.

10 So looking at the first question -- I'm sure
11 all of us have had a chance to glance over those --
12 "Discuss FDA's decision framework for selecting
13 strategies to manage a drug's teratogenic risk." And
14 it probably makes sense to bring the slide up when we
15 start the discussion so that we can all refresh our
16 memory what that framework looks like. Specifically,
17 discuss whether the framework appropriately reflects
18 all of the factors that should be considered when
19 determining how a drug's teratogenic risk should be
20 managed. So we are supposed to collect items in the
21 first part of this question.

22 And then in the second part, "Provide your

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1 recommendation as to which factors in the framework are
2 key for determining when labeling is sufficient to
3 manage the teratogenic risk, and provide your
4 recommendations as to which factors in the framework
5 are key for determining when a risk evaluation and
6 mitigation strategy is also necessary to manage the
7 teratogenic risk."

8 And I clarified with the FDA whether the
9 reference to REMS here means any type of REMS, because
10 we are aware that there are REMS that just include a
11 med guide. That's not the focus of this question
12 because a med guide, of course, is not that different
13 from labeling in terms of the way it imposes on
14 patients and providers and whoever else. And so the
15 focus of this question is really we are supposed to
16 distinguish between what key factors do we consider
17 should drive the decision whether there should be just
18 labeling or just a REMS with an ETASU.

19 All right?

20 Ms. Conover.

21 MS. CONOVER: Maybe this is more aimed for
22 Melissa, but I was concerned about the idea that

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1 something is teratogenic or it's not, that something is
2 safe or not, and I wondered how much risk certainty
3 there has to be to have one of these ETASUs implemented
4 where there are the more restrictive kinds of things
5 and how much human data would be sufficient to change
6 the program that you have or to initiate one, or what
7 kind of puts you over the threshold to start thinking
8 about having that kind of a risk management program or
9 in fact removing it as you start to have human data
10 that might reflect a different degree or risk? And
11 then actually number two is once that's decided, will
12 there be a retrospective effort? Because there are
13 many drugs, like methotrexate or something, that are
14 not on the list of things that have an ETASU but that
15 arguably are at least as teratogenic, I guess, as the
16 ones that do have it.

17 DR. MANZO: I'll try to address your
18 questions. While we don't require human data, and, in
19 fact, you saw lenalidomide didn't have any specific
20 human data, and there was a requirement for a REMS
21 because of its sort of structural association with
22 thalidomide, and in some of the other cases we often

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1 don't have human data at the time the drug is approved,
2 what we have is usually animal data, and in some of
3 those cases the decisions were made based upon animal
4 data. I can't get into the specifics of what sort of
5 animal data, I would have to have Melissa perhaps to
6 address that part, but it clearly doesn't require human
7 data.

8 And, I'm sorry, can you repeat what other
9 question?

10 MS. CONOVER: Well, that's okay. And if
11 there is subsequent human data, would that change the
12 way that you're approaching risk management then?

13 DR. MANZO: So if we have human data where we
14 don't see a signal, that I think is a little bit
15 touchier. We haven't actually removed any REMS based
16 on lack of human data, but it doesn't mean that it
17 doesn't exist. I mean, we know there is
18 underreporting, there are pregnancies that are
19 terminated, so at this time we have not actually
20 released any REMS based upon what we've seen in the
21 postmarketing setting.

22 MS. CONOVER: Because, as you know, many

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1 things that are teratogenic in laboratory animals
2 aren't in humans, and then as we gain human data,
3 sometimes we reevaluate risk. And I think what Janine
4 Polifka was talking about earlier was when you have a
5 fairly restrictive ETASU, or whatever, to use the
6 acronym, the implication to both physicians and their
7 patients is that this is a really dangerous drug. I
8 mean, it kind of is a red flag for real alarm, and so
9 it's one reason to back off on it if you have data that
10 suggests the risk is lower.

11 DR. MANZO: Thank you.

12 DR. TASSINARI: So let me just focus on the
13 dilemma of no human data and looking at the animal
14 data, and when do we make these decisions? I think
15 that this is where we go back to some forms of judgment
16 and looking at -- you're asking about, when is a risk
17 really a risk? And I know it's not fair, and I knew
18 you would ask the question.

19 The elements, for example, the elements that
20 lead us to conclusions about how concerned we are about
21 that data I think are well articulated in the
22 integrated process that anybody who works with this

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1 type of data goes through because, as you know, a
2 single event in a single study may be enough for you to
3 wonder if it's going to happen again but it's not
4 enough for you to make significant decisions.

5 Where we have confidence in our data is when
6 we see this iteratively, we see it in multiple related
7 circumstances. So this is the idea of the concordance
8 and the multiplicity across all of that, and our
9 confidence rises as we see that.

10 When we are talking particularly -- and I
11 think you've seen two examples this morning -- where we
12 are clearly working with products that have as their
13 central action receptors that we know are fundamental
14 to development, then we already know that that is going
15 to be a more significant piece of data for our concern
16 levels. And so there is a little art here, as you
17 know, but it is based on the data that we can
18 accumulate and the biology and timing and our
19 understanding of whether that particular dose in an
20 animal study has relevance to the human therapeutic
21 doses. All of this goes in, and that's why this
22 framework that we're looking at takes this into account

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1 when we are working with the scientific evidence for
2 this teratogenicity.

3 When we get human data and we're able to look
4 at this again, all the better, because we can then have
5 a much more confident view of that risk-benefit balance
6 that we're developing, and this is something that we
7 will continue to do, and I think we all have to do, to
8 prevent the scenario that you described, by having
9 information out there that isn't as effective in
10 allowing people to make good decisions about the
11 exposure to that drug.

12 MS. CONOVER: The other question was about
13 retrospective or including other agents that are not
14 currently under the approval process. All of us here
15 that do teratogen counseling can think of lots of other
16 agents that are a similar risk to the ones that have an
17 ETASU.

18 DR. KASHOKI: I just wanted to point out that
19 with regard to reevaluating what we have done in terms
20 of the teratogenic risk. This is not unique to
21 teratogenicity; it's the kind of approach that we would
22 apply to any serious risk that's associated with a

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1 drug, so we take the available information and so on
2 and so forth make our determination as to how best to
3 manage it, and then with subsequent information that we
4 may receive, we will then reevaluate the approach that
5 was previously taken, and Dr. Southworth highlighted
6 that point with regard to ambrisentan and Letairis and
7 the modifications that were made to the risk management
8 program with respect to hepatotoxicity once we had
9 specific information that gave us some sense of ability
10 to scale back on the risk management approach. So the
11 same sort of principles and practices that were used in
12 that instance and in other instances can be used with
13 regard to teratogenic risk.

14 DR. WINTERSTEIN: Dr. Morrato?

15 DR. MORRATO: I just wanted to continue
16 building along that, I think, line of discussion. I
17 guess as I react to the first question on the
18 framework, I might think about reframing it a bit and
19 how it might be used. So for me, I think it provides a
20 great opportunity for face validity, you know, to
21 answer directly the question I think you were getting
22 at, which is, why does this drug have a REMS with an

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1 ETASU and this one doesn't? So that it's very clear
2 and predicable to the degree.

3 So when I look at the intrinsic factors and
4 the extrinsic factors, I sort of view the intrinsic
5 factors as the ones that might be the ones related to,
6 is there a threshold that's achieved either in terms of
7 severity, frequency or expected incidence of the
8 teratogenic outcome or perhaps the patient population
9 that's using it is highly female of childbearing ages
10 and potential, et cetera.

11 I'm more worried in the extrinsic factors
12 being used to determine whether or not a REMS with
13 ETASU should be required or not because I think that's
14 what leads to the problems that we heard in the public
15 forum where you have, depending on the situation at the
16 time or the reviewers at the time or the precedent
17 within that one review division, you end up with a
18 highly diversified set of REMS, and then that sort of
19 undermines the face validity that you're trying to do.

20 So for me, for instance, the benefit that the
21 drug might have, I know that was mentioned in the
22 briefing materials, I see that as being used to weigh

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1 the decision of approvability. The risk is the risk
2 for the drug regardless of why the drug is being used
3 or how many people are using it or who is prescribing
4 it. So if the goal is to manage the teratogenic risk,
5 then we should be consistent with that is kind of how
6 I'm thinking of it, and that these extrinsic factors
7 then would be used to describe or to inform how to best
8 design the risk management program in light of how it's
9 used in practice, in light of who is using it, in light
10 of the provider setting, et cetera, but not used to
11 address the question around, should a risk management
12 be done?

13 And so the factors are involved I guess is
14 what I'm trying to say, but just sort of in a slightly
15 different way along that decision-making process.

16 DR. WINTERSTEIN: Dr. Hernandez-Diaz?

17 DR. HERNANDEZ-DIAZ: I think along the same
18 lines focusing on this aspect of the framework of the
19 teratogenicity of the drug, and it's related with the
20 current way of classifying the medications for the
21 label, and in the current system to some extent now
22 when we talk about the scientific evidence of

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1 teratogenicity, I think that we are mixing three
2 factors. One is the benefit for the risk benefit that
3 I agree I would put aside, but even within that benefit
4 part, in the risk, I think we are mixing the amount of
5 evidence with the strength of the risk. What I mean by
6 that is that sometimes we might have little evidence,
7 but we might believe that the risk is very strong, and
8 sometimes we have very good evidence, and within that
9 label of good evidence, we might know that we have a
10 medication that increases 100 times the risk of all
11 malformations or 200 times, like thalidomide, and we
12 might have pretty good evidence to believe that one
13 medication increases twofold the risk of one specific
14 defect that appears only 1 in 1,000.

15 So I think we have to differentiate the
16 quality or amount of evidence from the strength of the
17 association or the number of extra cases and severity
18 of the cases that we expect within the same factor.

19 And another related topic, I agree with this
20 complication of the decision, we seem to be applying
21 the decision-making to new medications coming into the
22 market, and we have not been doing the same with other

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1 medications that might have stronger risk. So I don't
2 know how we are going to deal with that. I think it's
3 an important point to discuss.

4 DR. WINTERSTEIN: Dr. Greene.

5 DR. GREENE: Thank you. I would like to
6 point out that in the list of 17 medications that we
7 have in front of us for which there have been some sort
8 of programs developed, I just rank-ordered them
9 according to the years in which the medications were
10 approved, and I notice that the first 10 were approved
11 in the years 1953 to 2000, so over 47 years there were
12 10 medications that entered into this program, and
13 since 2001, there have been 7. So I think that as we
14 have more medications that are targeted towards very
15 specific receptors and signaling systems, like Sonic
16 hedgehog, like trastuzumab, like gefitinib, we are
17 going to encounter more and more medications that
18 affect very fundamental processes in embryology and
19 development for which these kinds of considerations are
20 going to be very important, so that it seems that in
21 the near future, if we're consistent, this burden is
22 going to really snowball in terms of the number of

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1 programs, the numbers of medications, that we're going
2 to perceive the need for these programs for.

3 And in that light, I would like to ask the
4 question as to whether there is any evidence out there
5 that is sufficient to be really concerned about the
6 risk of women exposed to men on medication. Is that
7 something that we should really be chasing after? Is
8 there enough data in the literature in humans to
9 suggest that that represents a real risk? And if it
10 doesn't, is it fair to burden society, industry, with
11 chasing after what may not be a real concern?

12 We've been worried about this for some years
13 now, people have been studying it, the registries
14 include indirect exposures, quote/unquote, to men who
15 are some of these medications. I don't see a wit of
16 data or concern out there, and I wonder how much longer
17 we should continue to pursue that.

18 So those are my thoughts.

19 DR. WINTERSTEIN: Perhaps we could table this
20 for Question Number 2 because that's I think where we -
21 - but I will make note that we get back to this and
22 perhaps get answers.

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1 Dr. DiGiovanna, I think?

2 DR. DIGIOVANNA: I think compiling all of
3 these processes that have been used for different drugs
4 into a framework is not only very helpful, but I think
5 it's been elegantly done, and when that happens,
6 sometimes it shows where components have been done very
7 strong and where weaknesses are. And the weakness that
8 I see is in trying to assess any semblance of burden.

9 So I have two questions, one of which is,
10 what is the plan to try to address how to assess the
11 burden? And the second is that I'm a little bit puzzled
12 with those programs that already have a registry -- the
13 one I am, as a dermatologist, familiar with, is the
14 iPLEDGE registry -- where patients are enrolled, that
15 there should be some information, for example, about
16 which patients may have been enrolled but never filled
17 a prescription for various reasons or who had filled a
18 prescription and had been unable to comply with the
19 requirements at some point during the program and then
20 were either kicked out for a period of time and were
21 sufficiently able to enroll, or those who were never to
22 reenroll because that particular burden had become too

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1 much.

2 So I think some of that burden information
3 should exist with the registries that have been there,
4 and I wonder if anyone has taken a look at what the
5 existing information might have been, might be.

6 DR. SLATKO: So specifically on the access
7 and burden question. This is actually a fairly recent
8 and increased focus related to the more recent
9 legislation that we are tackling, and as part of a
10 broader initiative, we've already made public
11 statements that the FDA is looking at REMS assessments
12 more broadly, not specifically for teratogenic drugs,
13 and looking at a more comprehensive and rigorous way to
14 assess REMS performance. As you've heard, the
15 information historically has largely been in the area
16 of surveys of knowledge and understanding and in the
17 areas of outcomes, and we are seeking to fill in the
18 gap, if you will, of all the behavioral measurement
19 domains that may exist in between those extremes.

20 And in addition to the sort of effectiveness
21 metrics, as part of that work stream, we are looking at
22 assessment and burden metrics, and that's probably all

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1 I can say about it, but we would certainly welcome the
2 committee's feedback and ideas about what would be
3 viable ways. What metrics and what measurement systems
4 could you envision that we should consider as part of
5 our broader reevaluation of how we assess the
6 performance of these programs? Actually, it's one of
7 the questions that I think we have for you today.

8 So we would welcome that feedback either
9 today or as part of follow-up commentary from the
10 panel.

11 DR. WINTERSTEIN: Dr. Liebmann?

12 DR. LIEBMANN: So I think I'm like a lot of
13 people on the panel, that I'm a little bit frustrated
14 by the lack of data that we have to try to approach
15 some of these questions. In terms of the framework,
16 the framework, as it's been applied, has led to quite
17 different approaches to different drugs, with good
18 reasons. I don't think that it was arbitrarily
19 applied, but it's not clear to me, for example, why
20 vismodegib escaped a REMS apparently on the basis, at
21 least on the slide that we were presented, because
22 oncologists will appropriately counsel patients, but

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1 when lenalidomide and thalidomide, of course, are on
2 REMS even though presumably the same physicians are
3 approaching the patients the same way.

4 With that in mind, from the data that we
5 have, we have this very nice review, two of the drugs
6 in that review, mycophenolate and isotretinoin, were
7 not under either a RiskMap or a REMS for a number of
8 years before those were introduced. So do we have any
9 information from that review about incidents of birth
10 defects, unplanned pregnancies, or trying to look at it
11 the other way in terms of burden of a REMS? Was there
12 any change in prescribing patterns after the REMS went
13 in place for those drugs? Do we have any information
14 about that?

15 DR. KASHOKI: You asked about mycophenolate.
16 And what was the second one?

17 DR. LIEBMANN: Isotretinoin.

18 DR. KASHOKI: Isotretinoin.

19 DR. MANZO: Also, for isotretinoin, that drug
20 has been discussed at numerous advisory committees, and
21 the information that was presented at each of those was
22 data not only on the pregnancies that have been

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1 reported but on some information about mostly, I think,
2 as I recall, through surveys of whether patients
3 actually had pregnancy tests conducted, and were they
4 counseled? and so forth. So there definitely has been
5 information over the years that has led to a
6 strengthening of the program.

7 With regard to mycophenolate, I think most of
8 the data that we have for that product that led to the
9 decision was really around its comparative
10 teratogenicity with some of the other drugs that were
11 in the transplant registry itself, so it showed a
12 relative higher risk of teratogenicity than the other
13 products.

14 DR. LIEBMANN: I guess what I'm getting at
15 isn't just, gee, let's have a framework for REMS and
16 all that, the question is, is REMS effective? Is it
17 actually making a difference or is it just adding a
18 burden to the system? And do we have any data to tell
19 us that?

20 DR. MANZO: Well, I mean, that's difficult.
21 It's difficult to make those sort of comparisons. We
22 do have mycophenolate where we didn't have a program in

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1 place; we do now have it in place. It's only recently
2 been approved, so we really can't make any
3 determination at this point as to whether the REMS is
4 effective.

5 For isotretinoin, comparing before and after
6 is a little bit like comparing apples and oranges
7 because we do believe we're capturing more adverse
8 events than we did before the program, and so when we
9 presented the information last year, we didn't use the
10 actual pregnancy outcomes necessarily as a measure of
11 success, but that we were more certain that the safe
12 use conditions were being followed in comparison to
13 programs that were implemented for that program prior
14 to the current iPLEDGE program. Does that make sense?

15 DR. LIEBMANN: Well, again, this just
16 highlights, like I said, the frustration that we really
17 have no data. We're talking about using a framework to
18 design programs for which we have no idea if they're
19 going to achieve their stated goal.

20 DR. MANZO: That is correct.

21 DR. LIEBMANN: Okay.

22 DR. WINTERSTEIN: Dr. Shapiro?

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1 DR. SHAPIRO: I share some of that
2 frustration, but I also think that the question is hard
3 because the elements in the framework seem to be fine
4 for me, but it's really how they go together that I
5 don't think we've dug into the weeds to do that. So,
6 for example, if on the right-hand side, the
7 characteristics of the medical condition for which the
8 drug is going to be prescribed are horrible and severe
9 and long-lasting and the drug product is effective and
10 fairly safe for that condition and/or, going to the
11 left, if the impact on the fetus would be treatable or
12 minor, I mean, all these things, you weigh and balance
13 them differently, so just to buy into a framework
14 without doing that I think is not very helpful.

15 And it doesn't get to looking at the second
16 question, sorry, but, "Which recommendations are key
17 for determining when labeling is sufficient?" It might
18 be more appropriate to say "is better" because of the
19 access restrictions to a very good drug that might
20 happen if we don't do labeling and we do something
21 more.

22 So I think the questions aren't sophisticated

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1 enough, I think the framework isn't sophisticated
2 enough to weigh in. Sorry.

3 DR. WINTERSTEIN: Would you have specific
4 recommendations for a better framework? Because I
5 think Question 1 focuses on, are there any other
6 considerations that should be added?

7 DR. SHAPIRO: I don't know if you want to
8 take the time to go through guidelines for applying it,
9 but unless we do that, just in and of themselves, these
10 factors, and saying, "That makes sense," "That's
11 relevant," I don't find that helpful. If I were the
12 FDA, I wouldn't find that helpful.

13 DR. WINTERSTEIN: Dr. Polifka would be next.

14 DR. POLIFKA: I felt that the framework
15 really appropriately reflected most of the factors that
16 should be considered. And, in fact, in TERIS, the
17 TERIS database, we use those factors to consider risk
18 as well, but I found that membership in a drug class
19 largely influenced the risk management approach to be
20 disconcerting. And I understand that some of these
21 drugs, like ambrisentan, have a clear theoretical risk,
22 and the whole goal is to prevent adverse effects in the

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1 fetus, but I worry again about unnecessary terminations
2 of wanted pregnancies for agents like ambrisentan where
3 we have no human data, and we really don't know if it's
4 going to be harmful to the fetus.

5 And lovastatin is another drug where there is
6 a theoretical effect that it might affect the
7 embryonic/fetal biosynthesis of cholesterol, and it was
8 given a Pregnancy X category, but yet the human data so
9 far has been pretty reassuring.

10 So I think we have to be really careful about
11 using class effect as a factor to determine whether or
12 not a REMS should be applied.

13 And another factor that I thought should be
14 considered that I don't know if you normally do
15 consider, but I was wondering about whether or not you
16 consider the likelihood that a particular drug will be
17 used in combination with other drugs -- for example,
18 like anticonvulsants, usually women are on more than
19 one anticonvulsant -- and so if that influences the
20 risk management approach at all.

21 And then I was wondering if the fact that a
22 drug may have an effect on the hormonal contraceptive

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1 is considered at all. So if you take drug interactions
2 into consideration.

3 And then I want to echo what Mike was saying
4 about the exposure in semen, and there is no data so
5 far that I know of that really supports that this
6 should be a concern, so I, too, question whether this
7 is really worth having a REMS and requiring women of
8 men who are treated to be in a program.

9 DR. WINTERSTEIN: Okay. Dr. Chambers.

10 DR. CHAMBERS: I wanted to comment on what
11 Sonia said about looking at the magnitude of the risk
12 as a factor that's probably intrinsic, so not only the
13 biological plausibility, nonclinical data, and human
14 data, but weighing in on for many of these drugs that
15 have REMS now or labeling risk management approaches,
16 we don't know what the magnitude of the risk is, if we
17 even know it's teratogenic or not, so the magnitude of
18 the risk I would think would be an intrinsic factor
19 that should play a role, and also the magnitude of the
20 risk as it translates to the expected incidents in the
21 population. So a low-risk exposure like topiramate
22 might warrant a REMS because the number of exposed

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1 pregnancies is thought to be in the thousands, so maybe
2 you're adding 1,000 additional oral clefts even though
3 the magnitude of the risk is low. So I think that
4 should be a factor in thinking about this.

5 And extrinsic factors, I think the context of
6 the care is the point that was being raised before
7 about, are we assuming that because the woman is seeing
8 an oncologist that she is getting all the appropriate
9 risk counseling about contraception, and at least in my
10 experience, rheumatologists, oncologists, neurologists
11 know zip about counseling about contraception or how to
12 talk to their patients about contraception, and that
13 really the context of the care is that if it's anybody
14 other than a contraceptive counseling specialist who is
15 prescribing the drug, than that's probably not
16 something that should take it off the list, that we
17 assume that the health care provider is seeing the
18 patient often enough or in sort of a situation where
19 they can actually deliver that kind of information.

20 DR. WINTERSTEIN: Dr. Madigan.

21 DR. MADIGAN: I would just like to echo the,
22 I think, previous sentiments, that it's a step forward

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1 to right down a framework, it's very helpful, but it
2 sort of falls well short of a prescription for action.
3 And in some sense, I think what you would like to do is
4 put all of this in a formal decision theoretic
5 framework and weigh benefits and risks and
6 probabilities of various outcomes. I'm not so naive to
7 think that that's probably not feasible, but I think
8 there are parts of this that could be more quantified,
9 and in particular I'm thinking about the nonclinical
10 data. So in terms of lab data, and animal data in
11 particular, and especially data from multiple species,
12 there are certainly statistical frameworks for
13 combining information like that and coming up with the
14 posterior distribution for the true risk, for example.
15 So there is more in particular by -- this is not new
16 particularly. There is work by Bill DuMouchel that
17 goes back to the 1990s that does exactly this, formally
18 combines data across species and makes inference about
19 risk in humans, and with various assumptions, but the
20 beautiful thing is the assumptions are made explicit,
21 which they're not if we don't do this, and you get at
22 least some handle on, what degree of certainty do we

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1 have from these data?

2 So I guess my point is it seems that right
3 now none of this is quantified in any kind of formal
4 way. Perhaps parts of it could be quantified in ways
5 that might be useful.

6 DR. WINTERSTEIN: Dr. Polifka.

7 (No audible response.)

8 DR. WINTERSTEIN: I think we had it already.

9 Yeah.

10 Dr. Erstad?

11 DR. ERSTAD: My comments will be good, it
12 will take onto what Dr. Madigan was just saying.

13 First, I want to thank the staff for doing
14 this retrospective study where they are looking at how
15 the decisions were made with regard to risk management
16 because obviously if you don't do those kinds of look-
17 backs, you're not going to have any data on which to
18 base some of these decisions. So I guess my first
19 point would be to continue to encourage you to have
20 those kinds of look-backs that include surveys of
21 staff, et cetera.

22 But to take off on this point of decision

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1 analysis, you know, when I saw the framework again, I
2 thought for the most part it had the key things in it,
3 but I was wondering if this could be combined, whether
4 you look at it as a process chart or a decision
5 analytic kind of chart, where when FDA is presented
6 with a drug that has this potential risk, how the
7 decisions are made incorporating the various parts of
8 this framework. And I guess I would say I wouldn't let
9 the perfect get in the way of the good in the sense of
10 if I analogize to something we do in the hospital all
11 the time, is we take protocols, we know they're not
12 going to apply to 100 percent of the patients, we'll go
13 for 80 percent, and then we're willing to accept that
14 20 percent.

15 And so I'm looking at this, you know, the
16 response would tend to be, well, if we try to put in a
17 decision analytic kind of approach, there will be a lot
18 of parts that, you know, like the statement in here
19 where it's not just one factor but multiple factors,
20 but I think that could all be part of it. But if you
21 start to identify the processes and lay this out from
22 square one to the end in terms of some analytic

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1 approach, hopefully there might start to at least
2 appear to be more consistency and maybe over time
3 actually even develop more consistency, because again I
4 think the concern right now is there just appears to be
5 that for any given drug, things potentially are handled
6 in different ways, and I'm wondering if just as a start
7 of laying out the processes with these things
8 incorporated, and over time that could change, but
9 hopefully it might again begin to form some consistency
10 around some of the ways these decisions are made.

11 DR. WINTERSTEIN: Dr. Hernandez-Diaz?

12 DR. HERNANDEZ-DIAZ: I believe you wanted me
13 to mention the reference. Regarding the data
14 available, I feel the same thing, I don't think we have
15 enough evidence for each of the things that we would
16 like to know about REMS, including the (inaudible), but
17 regarding whether they work or not preventing fetal
18 exposures, so looking at the outcome as preventing
19 pregnancies, there is a New England Journal of Medicine
20 paper in 1995 by Allen Mitchell, et al., and one of the
21 initial pregnancy prevention programs for isotretinoin
22 showing how the program worked reducing the number of

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1 pregnancies, and also showing that when evaluating the
2 knowledge was not informative, that you really have to
3 go and evaluate the final outcome where there is a
4 reduction in pregnancies or not. So this is one that I
5 found that I can share with you later.

6 And since I have the microphone, I really
7 agree with Tina regarding looking at this, at the
8 amount of women that are going to be exposed because
9 that really wasn't any of the potential number of extra
10 cases, and it is discussed in the document that the
11 size of the population is important to consider, but
12 that it is unclear whether a larger size of the
13 population will support or not going for the REMS, so
14 just having the factor I know might not be very helpful
15 deciding the same thing as we were discussing before
16 regarding the indication, that it probably is REMS is
17 specific how to put all the factors in the equation to
18 decide.

19 DR. WINTERSTEIN: Is this in direct response?
20 Okay.

21 DR. CHAMBERS: I have a question about, is
22 the goal of REMS, a REMS in general, to prevent exposed

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1 pregnancies or is it to prevent birth defects? I guess
2 that's a question for the FDA because I think for
3 thalidomide and isotretinoin, it's to prevent exposed
4 pregnancies, but for drugs that we don't have any human
5 data, maybe it's to put a system in place that's to
6 prevent birth defects that we don't know yet occur in
7 humans.

8 DR. WINTERSTEIN: Well, but following your
9 reasoning, it seems that it really is the equation of
10 numbers needed to harm times the incidence of exposure,
11 and with this you get the total number of birth
12 defects; correct?

13 DR. CHAMBERS: Right.

14 DR. WINTERSTEIN: So I think that both of you
15 agree that if you take the total number of exposed, and
16 you take the excess risk, you get the total number of
17 birth defects.

18 DR. CHAMBERS: If you can predict what birth
19 defects will occur in humans, but for many of these,
20 you have no idea whether there is an increased risk --

21 DR. WINTERSTEIN: That goes on the evidence,
22 but I think, from what I understand, just trying to

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1 summarize, essentially what we want is that we feel
2 that a REMS needs to get as strong as we know the total
3 number of birth defects is large, and however that is
4 generated, whether it is a small population that is
5 taking the drug but the excess risk is tremendous or
6 there is a very large population who is taking the
7 drug, and the excess risk is not that much but the
8 effect would be the same.

9 DR. CHAMBERS: And the severity I think plays
10 a role as well.

11 DR. WINTERSTEIN: Of the malformation. Yeah.
12 Okay.

13 Dr. Fingert.

14 DR. FINGERT: I just wanted to get back to
15 the questions and ask the panel members as well as the
16 Agency if we should be addressing A and B together. So
17 A, it looks like you're seeking whether or not -- maybe
18 you could just clarify if I'm getting this right -- A
19 is you're seeking whether or not the framework, which
20 is on page 29 of the briefing document, reflects all of
21 the factors or if there are additional factors. And
22 then B is sort of like a -- so A is sort of

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1 quantitative and B is qualitative, if there are higher
2 sort of quality drivers in these framework that would
3 be key to support sufficiency of labeling as the major
4 way to manage teratogenic risk versus labeling plus
5 REMS. Am I getting these questions right?

6 DR. SLATKO: (Nods head yes.)

7 DR. FINGERT: Great. Thank you.

8 DR. WINTERSTEIN: Dr. Kaboli.

9 DR. KABOLI: Just in terms of a comment about
10 the framework, I mean, anybody that's either developed
11 a framework or worked with any sort of theoretical
12 framework knows they're imperfect and they're not
13 intended to be the final structure, they're supposed to
14 be the framework that you build upon. As I sort of
15 read through it and listened to the discussion, I think
16 it's actually a very good start. I think it's Version
17 1.0, and I think it's something that is an iterative
18 process, I think somebody else had mentioned it, you
19 know, that this is something that I think as you apply
20 it to existing drugs but also then applying it to
21 future ones that come up, you will tweak this and
22 you'll modify it, and some of the sections, some of

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1 them when I read through it, I really didn't understand
2 what it was, but I didn't need to right at that moment,
3 but I think in the context of specific drugs you'll
4 flesh this out over time. So I think it's a great
5 first start.

6 DR. WINTERSTEIN: Dr. Rasmussen?

7 DR. RASMUSSEN: I share the concern about the
8 dearth of data in two real areas. One is, how do these
9 REMS work? And then what is the burden? And I think
10 both of them, you know, just like when you look at a
11 drug, you're looking at the benefit of the drug, and
12 the risk, I think thinking of these REMS, we need to
13 think of, what is the benefit of the REMS and what is
14 the risk? And I think right now we don't have very
15 good data on either side.

16 And I was looking through last night at some
17 papers that have been published in this area, and there
18 are not very many even on Accutane, on isotretinoin,
19 which a lot of women take isotretinoin, a lot of
20 people, pharmacists, physicians, and patients are
21 burdened by the REMS, and yet we don't really know how
22 it works. And when I looked, there is a paper from the

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1 Journal of the American Academy of Dermatology that was
2 just published about a year ago that says that it
3 doesn't work and it was published by an HMO, and then
4 some of the other studies have been published by CDC,
5 but it doesn't seem like there are many other studies
6 out there. Why do people not do studies? Because
7 there is not funding. And I do wonder, how do we get -
8 - and I don't think there is going to be an answer for
9 this, but I do think if we're going to be committed to
10 women receiving appropriate treatment and keeping their
11 fetuses safe, we need to figure out a way -- we,
12 society, needs to figure out a way -- to fund this kind
13 of research or we're going to continue not having data
14 to say, is this REMS -- are the risks or the burdens of
15 this REMS worth the benefits that we're getting of
16 making babies more safe?

17 I guess the other thing is a comment about
18 the framework in general. I think it is a good start
19 and I really applaud FDA's efforts to try to do this. I
20 know how hard this is to have a big meeting like this
21 and how much work it is to do something like this. I
22 do think it is just a start and I think if I were

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1 sitting at the FDA trying to know what to do with this
2 framework, I'm not sure how you would really develop a
3 REMS based on this information. You might say, "Yeah,
4 I think we probably need one," but I think the next
5 steps of what it should be, I think, as the person down
6 there said, I think this is Version 1.0 and we have a
7 long way to go. So that's it.

8 DR. WINTERSTEIN: Dr. Whitaker.

9 DR. WHITAKER: I had my question a while ago
10 when we were talking about the actual elements and the
11 framework, and so I just wanted to say one thing about
12 the one element, the biological plausibility. I feel
13 like in the Hill criteria for causality, that's
14 actually our weakest criteria, just the plausibility,
15 and what I hear a lot of is it's biologically plausible
16 that this drug may cause this problem, it's
17 biologically plausible that a male taking the drug can
18 somehow cause a birth defect in his female partner, but
19 without the evidence, it seems like our balancing is
20 off to me, that we're putting a lot of burden on the
21 health care system and a lot of burden on our patients
22 based on this kind of plausibility idea, and biological

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1 plausibility should cause us to study things more but
2 not to implement restrictions.

3 So biological plausibility should cause
4 everybody to have all their patients who are on it be
5 on the OTIS registry or cause patient registries, but
6 that to implement REMS, especially with ETASU, where
7 you could actually be restricting use based on just
8 this idea that it might cause a problem is essentially
9 bad patient care, and it really concerns me that that's
10 like its own bullet on here and that it has such a high
11 level, that biological plausibility plays that high of
12 a role. So I just wanted to voice that concern.

13 And I'll just use the example. They gave the
14 example of the drug for pulmonary hypertension, and
15 this is a condition where pregnancy itself is
16 contraindicated, so you are actually withholding the
17 drug because she can't prove she's not pregnant, and
18 you want to avoid the exposure. If she's pregnant, her
19 obstetrician is mostly going to recommend a termination
20 regardless of her drug exposure. So that struck me as
21 an example where there was just really a disconnect
22 between the risk of the drug and the risk of the

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1 condition.

2 DR. WINTERSTEIN: Just to put this in context
3 -- and the FDA may want to correct me if I misread
4 that, I mean, the way -- I saw biological plausibility
5 pop up, but Hill criteria were quoted in the background
6 documents that we got, which go over all, over various
7 elements, how to look at causality and how to think
8 about causality, and, of course, here this is even
9 harder because we are stretching from animal studies to
10 human studies, but I think it's one component in
11 assessing whether there is a teratogenic risk or not if
12 we don't have essentially randomized clinical
13 experience that would answer this question definitely.

14 DR. WHITAKER: Can I just make one response?

15 DR. WINTERSTEIN: You're nodding. Okay, so
16 you're nodding.

17 DR. WHITAKER: Just this idea that once we
18 put them on, it's hard to take them off. So the
19 criteria should be stringent to put them on, and so
20 beyond just biologic plausibility, once we get the
21 human data, it's much harder to remove a REMS than it
22 is to put one on.

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1 DR. WINTERSTEIN: Okay. Dr. Cragan.

2 DR. CRAGAN: I agree with most of the
3 comments that have been said, and I think this
4 framework has most of the elements that are needed in
5 there, but I really want to make a plea that -- I mean,
6 I agree that the risk, the level of risk, and the
7 severity of the malformation should be the starting
8 place for this. As I've listened to presentations and
9 read through some of the background materials, I felt
10 like that kind of got lost in all of the factors that
11 you have to think about with a REMS, and I personally
12 feel like that should be the starting place, and then
13 you can look at what can be done in that setting, but
14 that there needs to be consistency with the way that's
15 applied and the way the known risk, the level of that
16 risk, the severity of the condition, is applied across
17 drugs to look at how that's managed, and then you kind
18 of get into what I consider the secondary details about
19 the rest of it.

20 DR. WINTERSTEIN: Dr. Morrato?

21 DR. MORRATO: I just wanted to add, after
22 listening to everyone, it would be helpful to frame

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1 this so that it's very clear sort of the threshold
2 effect of when you move from a labeling only to a REMS,
3 given the points you were saying, and within REMS, it's
4 REMS with education, similar to what Qsymia has, or
5 REMS with ETASU, which is very different. And it's
6 those step changes that I think people are looking for
7 guidance for, and I would support what everyone is
8 saying around the magnitude of risk or how risk is
9 mentioned. Because I just want to bring it back to the
10 article that you mentioned, Dr. Hernandez-Diaz, because
11 that was the one I mentioned, too, and if you look back
12 at it, the rate of 3.4 pregnancies per 1,000 was under
13 the context of a targeted education, signed informed
14 consent, and reminder tools. And if I remember
15 closely, roughly -- correct me if I'm wrong -- I think
16 what we heard from the iPLEDGE was that it was maybe on
17 the order of 1 pregnancy per 1,000 or something like
18 that. So, yes, it's better, but you're also looking at
19 the incremental, how better is it given the burden of
20 the restriction? And so it makes me wonder, it makes
21 it very hard to take something away now that it's moved
22 along that pathway, but it just makes me wonder if

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1 we've overshoot in terms of really what meets all of the
2 restricted ETASU versus whereas labeling and education,
3 where we're good enough, recognizing that society has
4 responsibilities, too. I mean, you can't overregulate
5 everything short of directly observed therapy, so there
6 is that balance on both sides.

7 So I guess my main point is when you write up
8 a framework, have it very clear, so what are these step
9 thresholds and how might someone then use this to
10 actually decide how to design their own program?

11 DR. WINTERSTEIN: Dr. Wisner?

12 DR. WISNER: I've been intrigued with this
13 discussion, and part of what intrigues me is the
14 Version 1.0, and it strikes me that when a decision is
15 made, should this be handled by labeling, by REMS,
16 ETASU, that there is a cross-sectional decision here.
17 And my thinking is going along the lines of, okay,
18 well, for Version 1.1 and 2, what is the information
19 collection here that we would need to move towards that
20 next version? And along those lines, I'm wondering,
21 given that a drug would get one of these designations
22 because there is concern and uncertainty, would there

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1 or has there been a requirement for some kind of data
2 collection, a mandatory registry, or some particular
3 structure so that the data to move to 1.1 or 2 is
4 identified?

5 DR. WINTERSTEIN: Dr. Fingert.

6 DR. FINGERT: Following the comments that
7 were just made, I'm very positive about the framework,
8 although I think it may be useful for us to consider
9 its history and context and the quality behind it. I
10 mean, to some extent, it's sort of like saying all
11 decision-making frameworks have uncertainty, but some
12 decision-making frameworks are useful. So, yes, it's
13 useful, but there is a lot of uncertainty here.

14 We heard about the sample selection criteria
15 this morning. In Section 9 of the briefing document it
16 talks about it being a retrospective review of the
17 selected 17, and as I'm hearing this, I see that there
18 is other criteria behind it, that the drug product
19 program I believe had to succeed and the company had to
20 continue marketing it so that there would be an active
21 REMS that happened or labeling that happened. So drug
22 product programs that were limited, that failed maybe

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1 in large part because of the REMS, or companies that
2 failed because of the REMS are not reflected here. So
3 you've got a selection of a denominator that we're
4 looking at, and I think we should be honest about that.

5 Some of you may know, it wasn't because of
6 teratogenic risk, but I know of at least one program
7 called Plenaxis was the product, and it was really a
8 very burdensome REMS that led to failure of the drug,
9 failure of the company, and we're not going to see a
10 speaker here from the Plenaxis company because the
11 company doesn't exist anymore because --

12 UNIDENTIFIED FEMALE SPEAKER: (Off
13 microphone.)

14 DR. FINGERT: I'm sorry, I forget. It was
15 for prostate cancer.

16 So I don't know if there are other programs
17 within companies that are not here either, that are not
18 represented, that failed.

19 So, I mean, I view this to some extent sort
20 of like level of evidence, if this was going to get
21 published in the Cotran reviews, that in a way it's
22 kind of expert opinion background, and a survey,

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1 selected survey. So as I understand levels of
2 evidence, that would be -- there are statisticians
3 here, please correct me I'm wrong -- that would be 3 or
4 4 as the level of evidence behind this framework. It
5 certainly would not be 1 or 2. And I think that it
6 might be useful for us to articulate that because -- in
7 a constructive way, that, you know, we call it 1.0
8 moving to 1.1 in the future. So it's a useful
9 framework with sort of limited support and sort of a
10 very, well, let's say, a limited background history,
11 and there is going to be certainly room to move forward
12 as we get more stronger evidence to support what to do
13 next as the decision-making framework.

14 Thank you.

15 DR. WINTERSTEIN: Dr. DiGiovanna.

16 DR. DIGIOVANNA: I have an addendum to my
17 question based upon what you said because it
18 recollected an experience that I've had with respect to
19 isotretinoin a number of years ago -- now unfortunately
20 maybe decades -- where I was invited to a meeting by
21 the people from Hoffmann LaRoche in Basel because they
22 had information about a new use for a retinoid for

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1 acute promyelocytic leukemia, and they had basically
2 felt that no one ever wanted to develop another
3 retinoid again given the difficulties that were posed
4 with developing such a drug, and they felt that it was
5 a, quote/unquote, humanitarian reason that at least for
6 this disease, which was largely lethal and had dramatic
7 response, to actually all-trans-retinoic acid, not 13-
8 cis-retinoic acid, that this line of evidence needed to
9 be pursued.

10 So my original question was the one thing
11 that I recognized was missing from this is a duration
12 or an expiration date or a time to actually reevaluate
13 whether or not the current regimen is still relevant,
14 but I do think it's important to consider that as a
15 burden, the difficulty with respect to the development
16 of large numbers of drugs that pharmaceutical companies
17 do not want to pursue because of the risk that they are
18 either not going to be accepted or are going to be too
19 financially improbable.

20 DR. WINTERSTEIN: Dr. Liebmann? Oh, sorry.
21 Dr. Hoeger.

22 DR. HOEGER: So actually I wanted to follow

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1 up on that because I was struck by one thing that was
2 brought up in the public discussion as well, is that
3 there is a migration of drugs over time to other uses
4 that open up in an entirely different population, for
5 example, methotrexate is now very widely used in
6 reproductive medicine and exposing much larger numbers
7 of women actually trying to get pregnant to this
8 medication, which is a very highly teratogenic agent
9 and probably very underreported based on our own
10 literature in reproductive medicine as far as how many
11 pregnancies are inappropriately exposed and
12 underreported, nobody puts case series together. So in
13 addition to the extrinsic factors, actual drug use
14 should probably be expanded because over time you may
15 see migration in populations, and therefore
16 reevaluation of that risk level.

17 DR. WINTERSTEIN: Okay. Thank you.

18 Dr. Greene, and then we are wrapping up and
19 move to Question 2.

20 DR. GREENE: At the risk of piling on, I
21 would like to point out that if we were running a
22 randomized controlled trial, there are rules for

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1 stopping for futility, and at some point when there is
2 a program and there is little, if any, evidence of
3 teratogenicity or effectiveness of the program, then
4 there would be reason to discontinue just for futility
5 because it's unlikely that if you continued the effort
6 indefinitely, you would reach a conclusion. So if we
7 want to be serious about limiting the burden of these
8 programs to the drugs where we think it really matters,
9 then we have to be sensitive to saying that at some
10 point it's futile and we ought to discontinue some
11 efforts that don't seem to be leading anywhere.

12 DR. WINTERSTEIN: Okay. Very last comment,
13 Dr. Menefee.

14 DR. MENELEE: I agree with Dr. Greene's
15 comment, that endpoints would be ideal, but at the same
16 time, it's sometimes difficult to know that because you
17 don't know if the REMS is effective and has prevented
18 those events from occurring or if the risk isn't there,
19 so it's hard to ever really truly make that
20 characterization.

21 DR. WINTERSTEIN: All right. So here is my
22 attempt to summarize everything that has been said, and

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1 please correct me if I misstate anything here.

2 There were a few preliminaries that I thought
3 are worth mentioning and put context to the discussion.
4 The very first one, incidentally, started with Dr.
5 Greene's statement that the burden of risk management
6 seems to increase and the burden of managing
7 teratogenicity seems to increase or it is definitely a
8 very timely topic and probably something that we feel
9 the FDA will wrestle with for a longer time period.

10 There was also an expression of lack of data,
11 and lack of data on a variety of different issues, one
12 related to the risk, the teratogenic risk, altogether.
13 So the issue with how do we impute animal data, how do
14 we translate animal data, to clinical data, and how do
15 we handle the fact that the data may not be good enough
16 to really support decision-making?

17 The second part was data on the effectiveness
18 of the REMS as such, and, in particular, how much of
19 incremental gain does a more restrictive REMS give us
20 considering the burden that comes with it and the
21 potential access issues that are imposed with it? And
22 it seems that those two really need to be quantified so

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1 that a risk-benefit decision can be made.

2 And I think that brings us to essentially
3 what we're dealing with, is a risk-benefit decision of
4 the management of a drug where we need to make a risk-
5 benefit decision as well. So it's risk-benefit of
6 risk-benefit more or less, and I think that's what
7 makes it so complicated.

8 Okay. So we need data, we need more data on
9 the teratogenic risk, we need more data on the
10 effectiveness of REMS and the various types of REMS,
11 and we need more data on the burden of the REMS, and
12 then we need to put all of this together in a more
13 explicit and more statistically involved framework to
14 try to come up with some quantitative means of weighing
15 all of this.

16 It was also mentioned that the framework that
17 is suggested seems to cover the key areas that should
18 be considered when deciding on REMS, but it also
19 appears that this framework is superficial and really
20 deserves more explicit guidelines so that it becomes
21 more useful, and those explicit guidelines, of course,
22 again really relate to the evidence that we need and

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1 that may not be completely available.

2 So looking at the issues that came up as the
3 more important ones to be considered when we're
4 deciding on the types of REMS, I think the number one
5 that was mentioned by various members is we really need
6 to look at the total number of people or children who
7 would be harmed, and that is really the equation of the
8 total population at risk or the total number of people
9 who would be exposed times the numbers needed to harm,
10 so basically the severity of the teratogenic risk that
11 we are dealing with -- sorry, the size of the
12 teratogenic risk we are dealing with, and then times
13 the severity of this, so there may be minor
14 malformations versus very significant issues. And all
15 of this, again, it would be easier if that were
16 quantifiable so that it can go into a more informed
17 decision framework.

18 The second issue was that the strength of
19 evidence is currently very often mixed with the
20 strength of risk, that again deals with data, and that
21 that needs to be a more carefully considered framework
22 and it needs to be teased out so that we really know

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1 what we're dealing with.

2 The third was -- or I mentioned this already,
3 yeah, but this was another issue that came up a lot, so
4 I will reiterate this -- that we really need to weigh
5 the incremental gain of a more restrictive REMS and the
6 safety that comes with it against the burden.

7 And then the final point that I thought was
8 important that leads very nicely into another part of
9 the discussion we will have later this afternoon was
10 Dr. Morrato's statement of risk is risk, no matter what
11 kind of indication, and that might be something we may
12 want to continue to discuss as we move to I believe
13 it's Question Number 3, but that deals with whether it
14 really doesn't matter what kind of indication is
15 treated with a particular drug, at the end of the day
16 we are still dealing with a total number of children
17 who are malformed, and that is essentially the key
18 piece in all of this.

19 Does this summarize the discussion?

20 (No audible response.)

21 DR. WINTERSTEIN: Good. Wonderful.

22 Then we are moving to Question Number 2, and

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1 I will try to pay attention.

2 So Question Number 2 is, "Discuss the
3 adequacy of the current definition of females of
4 reproductive potential and whether the definition
5 includes the necessary identifying characteristics. The
6 definition of females of reproductive potential is
7 girls who have entered puberty and all woman who have
8 uterus and have not passed through menopause."

9 And then perhaps we can take on to this, and
10 that is Number 3, "Under certain circumstances,
11 females, either pregnant or of reproductive potential,
12 who are partners of male patients taking a teratogenic
13 drug can be considered at-risk populations. Discuss
14 whether evidence or considerations are important for
15 determining when these groups are at risk."

16 And this brings us back to Dr. Greene, and
17 maybe we can answer now your question, what is the
18 evidence that the exposure of male partners and the
19 resulting birth defects is really an issue or not? And
20 then move on with the discussion of whether we like the
21 definition of "at risk" right now as it is proposed by
22 the FDA or used by the FDA right now or whether there

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1 are recommendations for revision.

2 Dr. Polifka?

3 DR. POLIFKA: So I was just going to say for
4 Number 3, I think that these women can be considered to
5 be at risk when I think it can be demonstrated that
6 levels of drug found in the semen and cervically
7 absorbed are high enough to interfere with embryonic
8 development. And so I think if there is evidence that
9 can be shown, then we can maybe decide that these are
10 women who are at risk, but until then --

11 DR. WINTERSTEIN: So the question is, is the
12 evidence -- right? Does the FDA want to comment on
13 that?

14 DR. TASSINARI: So if I understood what Dr.
15 Polifka just said, she just provided us with her
16 suggestion of what the level of evidence should be to
17 make a decision to apply the term "at risk population"
18 to this group of women. Is that what I heard?

19 DR. POLIFKA: (Nods head yes.)

20 DR. TASSINARI: That's what I've heard.

21 I'm wondering if you could speak a little
22 further as to what one might do in the absence of or in

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1 the interval of time when we're trying to get that
2 information.

3 DR. POLIFKA: Well, I think that maybe that's
4 when a label comes in handy, is just to say there is
5 this possibility, but until there is any evidence, I
6 think you can only counsel women that they're probably
7 not at risk or that their risk is very low.

8 DR. WINTERSTEIN: Dr. Chambers?

9 DR. CHAMBERS: I'm ignorant about the
10 preclinical testing, but is it possible to incorporate
11 that as one of the preclinical endpoints?

12 DR. TASSINARI: Could we have Dr. Reid join
13 us and possibly answer that question?

14 DR. REID: Lynnda Reid, Division of
15 Reproductive and Urologic Products.

16 And right now we don't find that the
17 nonclinical models are really very beneficial for this.
18 They can tell us that there is a teratogenic risk, but
19 they cannot really tell us how much might be in the
20 semen. And in our division at least, we ask for semen
21 studies in men to determine the amount of drug, and
22 then we do a risk assessment based on if even 100

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1 percent of that level were available to the fetus,
2 would there be a problem with it? And our biggest
3 problem is with drugs in which we have no NOAEL level,
4 and we don't know what the risk is even with tiny
5 exposures.

6 DR. WINTERSTEIN: Dr. Francis?

7 DR. FRANCIS: Yeah, I just wanted to make a
8 couple of comments, and I apologize because I guess I
9 wasn't being seen over here, but getting back to the
10 first question, can I just add? Because one of the
11 things that I heard a number of people say was that
12 they applauded FDA for actually putting something on
13 paper, and I just want to echo that, having been at EPA
14 for over 30 years, I know what it's like to try to
15 develop guidelines for the first time, and I know that
16 that's a very difficult thing to do, being from a
17 regulatory agency, and I think it's really nice that
18 they were able to begin the process.

19 And just as at EPA, it is an iterative
20 process, and we all recognize that, and that as more
21 and more data become available, you'll be able to take
22 the documents and tweak it and improve it and make it

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1 more useful, not only as more data become available but
2 also as more tools become available, and I know we've
3 heard some people talk about some of the latest tools
4 like apps and things like that that 5 years ago, 10
5 years ago, really weren't there, and as we begin to
6 make better use of this, I think we might wind up with
7 the type of quantitative data needed to be able to take
8 this away from being more using professional judgment,
9 which I see a lot of that and hear, to actually being a
10 bit more quantitative.

11 But then I wanted to get back to the point
12 that I just made, and I was struck -- I wanted to make
13 the same comment that Janine did about it's not only
14 the presence in the semen but it really needs to be at
15 a level that would be of concern, and I think we just
16 heard from Dr. Reid that they actually have data as to
17 whether it may or may not be in semen that they get.

18 And that's the other thing that struck me,
19 because I've heard a number of people say that there
20 wasn't enough information here regarding I guess the
21 concern for hazards. And clearly coming from an EPA
22 standpoint, where we have very little data, I mean, I'm

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1 just amazed at the data that you have, and yet there is
2 a feeling that you don't have enough.

3 (Laughter.)

4 DR. FRANCIS: We've made lots of decisions on
5 a lot less data, and I know at some point you need to
6 make those decisions as to how you could take that
7 information and make inferences between the animal
8 data, but there is a lot of information out there,
9 there is a lot of background data documents that
10 describe how to integrate the data that FDA provided
11 that are done at an international level, and I think
12 making use of all this information and putting it into
13 a weight of evidence approach is going to be critical
14 to be able to make those key decisions.

15 DR. WINTERSTEIN: Dr. Morrato.

16 DR. MORRATO: Yeah, I know a lot of the
17 briefing material was talking about drugs that were
18 excreted via semen. I was wondering if there is a
19 point of view at FDA with regard to topical, so, for
20 instance, AndroGel, and I've seen advertisement or
21 communication that is very focused around the risk
22 management of exposure to women from where the men are

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1 putting the gel on, et cetera. So I didn't know if
2 that fell within, as you were talking, these.

3 And then the only other point, I really, I
4 guess, wanted to reflect what the industry
5 representative had that was his Slide RM12, I think. I
6 guess I like the definition that you have down here,
7 but whatever definition so that it's used consistently
8 across all the REMS. I forget the word he used --
9 "surprised," "shocked," "alarmed," "upset," whatever --
10 that there are so many definitions of what they were
11 aiming for across the REMS even of most recent, how
12 they were defining women of childbearing potential. So
13 hopefully we'll consolidate back to a common definition
14 then.

15 But I didn't know about the topical. Does
16 that -- yeah, so this is the one, I guess. I don't
17 know if it would be useful. I haven't compared these
18 listings to what you have suggested with the FDA. Does
19 it all fit under the same framing or just debating as
20 to what postmenopausal is, if it's 24 months, 12
21 months, what young age, whether it's a Tanner stage or
22 how you define that? Are those the main distinctions

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1 between them? It's more the definitional operation of
2 you have now entered puberty or you've passed through
3 menopause? Is that the main differences?

4 DR. TASSINARI: Let me see if I can go there.
5 This, I think, is a very effective slide to explain why
6 we brought a definition here today. These REMS have
7 been in place over many years, and for very good
8 reasons on each of those individual decisions, there
9 was a definition that was created. But it has become
10 clear to us that we needed something more universal,
11 and so we really are looking forward to your comments
12 on how we have settled on a definition that we wish to
13 use going forward.

14 DR. MORRATO: So are you looking for feedback
15 on how to define then, in quote, entered puberty or --
16 you know, because some of these seem to be trying to
17 quantify how you define you've entered puberty or how
18 you define you've passed through menopause. Is that
19 what you're looking for feedback or just that
20 conceptually this sounds good and you'll go away and
21 say, how do we put a number to that or a measure?

22 DR. TASSINARI: I think the short answer is

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1 yes.

2 (Laughter.)

3 DR. MORRATO: I'm not a clinician, so I can't
4 comment on it, but maybe others could speak to that.

5 But how about the AndroGel question? Does that fall
6 within the at-risk as well or are you only considering
7 ones that are excreted in semen?

8 DR. TASSINARI: So I'm not sure we were
9 thinking about transdermal exposures when we were
10 working on this, but just enough to say that sort of
11 the same concepts or the same thought process I would
12 think would fall into play with a transdermal versus
13 some of the questions that we have here. But, no, I
14 don't think when in constructing this we were thinking
15 about transdermal exposures.

16 DR. MORRATO: Yeah, I would follow the same
17 principles that others have been mentioning on how to
18 make the determination, I just wouldn't be so narrow
19 that it has to be a certain way of delivery, that that
20 way it might be more long-lasting.

21 DR. TASSINARI: Yeah.

22 DR. WINTERSTEIN: Ms. Conover?

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1 MS. CONOVER: And, you know, actually just to
2 add briefly to that, those medications that are used
3 for prostatic hypertrophy that women are not supposed
4 to handle their husband's medications, we all at the
5 teratogen projects get those calls about how dangerous
6 that might be.

7 But my question was actually whether you
8 would also include paternal exposures as in
9 preconception paternal exposures, because I think there
10 is at least -- of course, the data is not great on that
11 either -- at least as much data on that as there would
12 be on excretion in semen and risk to the fetus.

13 DR. TASSINARI: Thank you.

14 DR. WINTERSTEIN: Dr. Hoeger?

15 DR. HOEGER: So I was just going to the
16 second question, so I can either wait or we can go
17 forward, just with respect to menopause, and I think I
18 would clarify this just as this is unintentional
19 pregnancy I'm presuming because menopause is no longer
20 an obstacle to getting pregnant. I have many patients
21 in my clinic who are on teratogenic drugs coming to me
22 for (inaudible), so that's not a block, but it's not

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1 going to be unintentional.

2 DR. WINTERSTEIN: Dr. Menefee?

3 DR. MENELEE: So my question is on Number 2,
4 and I guess we can assume for a moment that we have a
5 clear definition of what puberty is and what menopause
6 is. I guess the current definition is pretty all-
7 comprehensive, all women of reproductive capacity, and
8 that's clearly for safety purposes. But I'm wondering
9 if it's more comprehensive than it needs to be. For
10 example, if you have a woman of reproductive capacity
11 and she is getting contraceptive under the care of a
12 physician, for example, an intrauterine device or Depo,
13 medroxyprogesterone, something that is administered by
14 the physician, something that is very effective, has a
15 low failure rate, it would seem that that individual
16 would have a very low risk of pregnancy, lower than
17 someone that is taking an oral contraceptive or using a
18 barrier mechanism. So is it necessary to subject that
19 person to all of the requirements of a REMS?

20 DR. WINTERSTEIN: Dr. Fingert?

21 DR. FINGERT: Well, I'm not really sure, in
22 following Dr. Menefee's last thought, that the question

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1 here really has to do with decisions about REMS for
2 this population. I thought it was a more simpler
3 technical question about the adequacy and parameters
4 for these definitions that are being used. Am I right
5 on that?

6 (No audible response.)

7 DR. FINGERT: Okay. Because I would like to
8 raise the point about getting back to something you
9 said earlier about the ability and the intent to seek
10 other input because I think you also made the comment
11 earlier about getting advice or thoughts from us about
12 how to do that, where to go. I know there is a Society
13 for Reproductive Medicine that's grappled with this,
14 and I think in terms of clinical research studies for
15 enrollment to protocols and how these things are
16 managed to protocols, groups like the CTTI, the
17 Clinical Trials Transformation Initiative, is now
18 working on this as well to provide recommendations.

19 Because if you think about it, the people
20 that are investigators also become prescribers, and it
21 certainly would be useful, in my view, to seek
22 alignment for how these things are decided and used.

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1 Otherwise, you may end up with a lot of confusion or
2 lack of compliance just because one day they're told to
3 define things one way and the next day they're told to
4 define things another way. I think it's the kind of
5 thing that could be done with better alignment going
6 forward with groups like that being part of the
7 dialogue.

8 DR. TASSINARI: Thank you.

9 DR. WINTERSTEIN: All right. I think we can,
10 right before the break, summarize that I think the
11 panel applauds the FDA to find a standardized
12 definition for the population at risk. I think that we
13 all feel that the framework is appropriately defined,
14 that the definition of puberty and uterus might be
15 aligned with other definitions that have been used by
16 other societies and that the panel doesn't need to have
17 more input on how the exact final definition might look
18 like.

19 With respect to Question Number 3, my sense
20 was that the panel feels that there is very limited
21 information on the risks that might be imposed by
22 exposure of women indirectly through their male

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1 partners and until that is answered, it is very hard to
2 make a decision, which is, of course, what the FDA
3 feels as well, and so we haven't really answered this,
4 if I have framed that correctly or if I have summarized
5 this correctly. So this is a, "More data is needed,"
6 answer that you are getting from us.

7 I see nodding.

8 Yes, Dr. Liebmann.

9 DR. LIEBMANN: So I agree that more data are
10 needed. In the absence of data and getting back to the
11 issue of biological plausibility, though, does the
12 issue of partners of male patients fail the biologic
13 plausibility test? I realize that we weren't going to
14 take a vote here, but I would actually be curious to
15 know if we took a vote, would most people say, "Why are
16 we doing this? Why are we insisting that men have to
17 go through this?"

18 DR. WINTERSTEIN: Yeah. The reason I phrased
19 this like this, I was thinking about our answer to
20 Question Number 1, and it seems in Question Number 1 we
21 have made a very strong point about how the strength of
22 the evidence and the strength of the risk and the

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1 severity of the risk really needs to be quantitatively
2 assessed in order to come up with a standardized
3 fashion to select then the adequate REMS for this, and
4 I think that it seems that this issue very nicely fits
5 into this framework because if that risk is defined,
6 then it's also clear what kind of REMS should follow.

7 Yes?

8 DR. LIEBMANN: And I agree with you
9 completely. It again just gets into looking forward in
10 real time over the next several years, there are going
11 to be more drugs approved, more REMS programs, and a
12 lot of these issues that we would like data for we
13 aren't going to, and so the question is, how are these
14 going to be structured in real time in the next few
15 years? And so again I just think that it sounds like,
16 from what I've heard in this conversation, that in real
17 time in the next few years a substantial body of this
18 panel would feel that it's not necessary.

19 DR. WINTERSTEIN: Dr. DiGiovanna?

20 DR. DIGIOVANNA: To follow up on that, just
21 for a point of clarification for myself, as a
22 dermatologist who does work with occasionally the

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1 iPLEDGE program, and I'm not familiar with how many
2 other REMS have a component where males are required to
3 actually register, have there been any cases that have
4 been identified where pregnancy has occurred and there
5 has been an adverse event associated with a male who
6 has been registered?

7 DR. WINTERSTEIN: There was I think one that
8 was reported on one of the earlier slides, wasn't
9 there?

10 DR. LIEBMANN: With a normal outcome.

11 UNIDENTIFIED FEMALE SPEAKER: Yeah.

12 DR. WINTERSTEIN: Yeah, there was a
13 pregnancy.

14 DR. DIGIOVANNA: So are these programs ever
15 evaluated and then ratcheted back to less restrictive?
16 Has it ever happened? And how does it happen? I
17 guess, how would something like that be removed, or
18 could it be?

19 DR. MANZO: Well, certainly it could. I
20 mean, if the sponsor has some additional data, I
21 suppose, where they felt that there wasn't a risk for
22 the partners of male patients who might be taking the

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1 drug, there could be a proposal to remove certain
2 components of the REMS. For a lot of these, though,
3 there is a level of burden for males in any case, at
4 least even in the case for isotretinoin where male
5 patients, at a minimum, have to be enrolled into the
6 program, have to undergo at least some counseling to
7 begin with but may not require, obviously, some of the
8 other components that the females are required to do,
9 such as pregnancy testing, contraception, that sort of
10 thing.

11 So, I mean, one of the questions we also had
12 for you was what would be the benefits and/or issues
13 that might arise if we made some of these programs more
14 targeted to that risk population, however that
15 population is defined?

16 DR. WINTERSTEIN: Dr. Greene?

17 DR. GREENE: There are more than one negative
18 study actually. The ribavirin exposure study,
19 postmarketing surveillance study, looks at, quote,
20 indirect exposures via treated men, and there is no
21 evidence of teratogenicity in those pregnancies that
22 were indirectly exposed to ribavirin via semen from men

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1 who were treated for hep C.

2 DR. WINTERSTEIN: What was the sample size or
3 what was the number of --

4 DR. GREENE: I knew you were going to ask me
5 the denominator, and I can't remember it. I apologize,
6 but there is no evidence of teratogenicity in the cases
7 that have been enrolled in the postmarketing
8 surveillance study. I could look it up for you and I
9 can get it for you.

10 DR. WINTERSTEIN: Dr. Polifka? I just wanted
11 to make sure that I did not skip somebody on the list
12 here. Sorry.

13 DR. POLIFKA: That's all right. I apologize
14 to keep harping on this, but to follow up on what Dr.
15 Greene just said, there are published cases of
16 ribavirin exposure where the couples were advised by
17 the physicians to terminate a wanted pregnancy because
18 the husbands had been exposed to ribavirin. So I think
19 that's something that should be taken into
20 consideration.

21 DR. WINTERSTEIN: Dr. Fingert?

22 DR. FINGERT: So Dr. Manzo just raised an

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1 interesting possibility about how it's possible for a
2 sponsor or even the Agency or any stakeholders to
3 ratchet back a REMS program. And earlier the question
4 was raised from panel members, can we think about
5 moving forward in a way to have a futility analysis?

6 I would like to ask the Agency, in the past
7 18 months or so, have there been examples where any
8 kind of REMS program has been ratcheted back? And if
9 so, is that a topic we want to talk about for how it
10 could be possible even for a teratogenicity?

11 To be honest, I'm asking a question, I know
12 the answer, that there have been REMS programs, but not
13 teratogenicity based, that have been cut back, and I
14 thought it was kind of a milestone because we heard
15 earlier about how some sponsors are so reticent to
16 develop and institute a program because they think
17 they're committed to it forever. So understanding that
18 something might be needed for a few years to get more
19 data, have more comfort, more certainty about a
20 program, but just for a few years is sort of a
21 different mindset than something they're committed to
22 forever.

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1 So I'll get back to my question. My question
2 is, have there been examples where the Agency has
3 agreed to cut back on a REMS program in general and
4 should we talk about that kind of possibility happening
5 as well for one that's implemented because of a concern
6 about teratogenicity?

7 DR. MANZO: There was an example that was
8 presented this morning by Dr. Southworth for Letairis
9 where we ratcheted back on the hepatotoxicity
10 monitoring and actually took those warnings out. I
11 think one thing that we do want to do is make sure that
12 we get some of these questions addressed. I mean, we
13 understand a lot of interest and ratcheting back REMS
14 in general, we do want to sort of try to focus it in on
15 the teratogenicity risk if we could, and to the extent
16 that we can have those questions answered, I think
17 that's where we would like to get some input from the
18 committee.

19 DR. WINTERSTEIN: Yeah. On that note, I
20 think we can close the discussion on Question Number 2
21 and 3 in particular since a similar topic will be
22 addressed in Question Number 4. So I would like to

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1 call for a short break now so that we can all refresh
2 our brains.

3 We will take a 15-minute break. Panel
4 members, please remember that there should be no
5 discussion of the meeting topic during the break
6 amongst yourself or with any members of the audience.
7 We will resume at -- can we do 3:25 so that we stay a
8 little bit on time? Thank you.

9 (Break from 3:09 p.m. to 3:27 p.m.)

10 DR. WINTERSTEIN: All right. Do I have to
11 say anything? No. Questions to the Committee/Committee
12 Discussion (Cont)

13 DR. WINTERSTEIN: Now, we are not completely
14 off the hook with regard to Question Number 3. So,
15 everyone, please consider this scenario, and I think
16 that's really an important scenario to think about
17 after the FDA described it to me. So assume that there
18 is actually a proven teratogenic risk and there is a
19 proven threshold based on animal data or human data or
20 whatever that has been evaluated in women, and assume
21 that for in the approval process the FDA would also
22 require a semen analysis, and in this semen analysis,

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1 one would find that there is a concentration of the
2 drug in the semen that meets this teratogenic
3 threshold, so essentially the exposure to the women in
4 utero would be similar to a drug concentration that has
5 shown already to be teratogenic. Under those
6 circumstances, would you consider that the population
7 at risk should include the partners of men who are
8 taking a drug that is teratogenic?

9 Dr. DiGiovanna.

10 DR. DIGIOVANNA: May I ask a clarification
11 question?

12 DR. WINTERSTEIN: Yes.

13 DR. DIGIOVANNA: You're saying that the
14 concentration of the drug in the semen would be
15 sufficient to give a blood level in the mother that is
16 at risk or the concentration in the semen is the at-
17 risk level? So it would have to be then again absorbed
18 and be at that blood level in the mother.

19 DR. WINTERSTEIN: That would be the question,
20 how it now gets to the fetus basically -- right? --
21 whether it's via blood or whether there would be any
22 other means of absorption I suppose?

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1 Yes, please.

2 DR. YAO: So if I could provide some
3 clarification. So the issue really is we recognize
4 that for the purposes of consideration of that risk for
5 the implementation of a REMS, we've heard from you that
6 biologic plausibility by itself doesn't really cut it,
7 you've really got to have something else. And as we
8 heard from our pharm tox colleagues, it's hard to get
9 nonclinical data. Sometimes nonclinical data don't
10 even apply.

11 But in the situations in which we believe
12 there is biologic plausibility for which the teratogen
13 doesn't really have a NOAEL, that at any level in the
14 patient it could be considered a teratogen, then what
15 evidence do you need? And one option we've heard is to
16 assess the level of drug in semen. Now, that doesn't
17 tell you that the level in semen will actually directly
18 be completely 100 percent absorbed by the woman, and so
19 what level or what types of things are you really
20 saying here would be necessary for us to consider this
21 population at risk or there isn't anything? And
22 specifically the issue of, should we be doing semen

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1 analysis on men and what level in semen would be
2 considered sufficient in terms of a level that you know
3 in a woman if she had that level were to potentially
4 produce teratogenicity? That's the complicated
5 question.

6 DR. WINTERSTEIN: Dr. Polifka.

7 DR. POLIFKA: Well, so my answer to that
8 would be that the level, the blood level, in the mother
9 has to be a concentration that's known to be
10 teratogenic. And I disagree that any level is
11 teratogenic. I mean, we know from teratology research
12 that teratogenicity is dose-dependent, so just because
13 you can measure a drug or a chemical in semen or blood
14 or whatever doesn't mean that it's going to be
15 teratogenic.

16 DR. TASSINARI: So herein I think you can see
17 where our dilemmas and questions are and why we're
18 asking you all, as experts, how you view this, and that
19 is, in those circumstances, for example, where we have
20 evidence that the drug might be in semen and we might
21 even get a level, how do we factor that into the
22 considerations that we have? Because once it's there,

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1 you have a potential for this.

2 So what are you looking for? And in the
3 absence of that data, how should we be acknowledging
4 this information so that people can make decisions?

5 DR. WINTERSTEIN: Dr. Whitaker?

6 DR. WHITAKER: I am wondering if there is any
7 other evidence ever of semen concentrations, any drug
8 getting into a woman's bloodstream like outside of
9 reproductive health where we've seen any kind of
10 adverse event, like is this just a case for
11 reproductive drugs or is there actually some
12 (inaudible)? I don't know of any case of a man being
13 on a drug that got into the woman's bloodstream to
14 cause any effect in any situation, whether it was a
15 known good effect of the drug or a bad effect, an
16 anaphylactic reaction? So I just want to raise this,
17 is this only an issue that's come up for reproductive
18 drugs, or is this an issue that's sort of new on the
19 table for other adverse events?

20 DR. TASSINARI: I'm not sure I can answer
21 that question, but I think ultimately what we're
22 concerned about is exposure to the fetus. So it's not

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1 necessarily that the drug might get into the woman's
2 bloodstream but that the fetus might be exposed by
3 whatever means. So that's part of this question as
4 well. As far your actual direct question, I'm not sure
5 I know the answer to that.

6 DR. WINTERSTEIN: Dr. Chambers?

7 DR. CHAMBERS: Just to toss an approach out
8 there, I guess I would feel like if there was a
9 theoretical risk, perhaps with something like
10 isotretinoin or thalidomide, you could make a case for
11 there being a theoretical risk, that maybe it should be
12 something included in the label as a theoretical risk,
13 but until there is even a single case report of a male
14 exposure where the female was also exposed where the
15 child has the embryopathy, I think there is no evidence
16 that exposure mediated through male semen has induced a
17 teratogenic effect for any drug.

18 DR. WINTERSTEIN: Dr. Conover?

19 MS. CONOVER: Well, I would agree it's not
20 one of my huge concerns when I'm answering teratogen
21 questions, but I also don't think there is much human
22 data suggesting -- I think -- I'm not aware of hardly

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1 any studies where they actually looked at male use of a
2 medication during pregnancy and looked at the outcome
3 of the fetus.

4 DR. CHAMBERS: Yeah, but you would expect --
5 sorry -- you would expect for something like
6 isotretinoin that a kid, a child, with isotretinoin
7 embryopathy whose only exposure was through the male,
8 that it would have ended up as a case report in the
9 literature somewhere in the 20 years the drug has been
10 on the market.

11 MS. CONOVER: (Off microphone comment.)

12 DR. CHAMBERS: That's true. Yeah.

13 DR. WINTERSTEIN: Dr. Polifka?

14 DR. POLIFKA: So my question for you,
15 Melissa, is, are you going to require REMS for all
16 drugs that are topically applied? Because we don't
17 know how much is always going to get -- we don't know
18 how much systemic absorption there is. Do we have the
19 same level of concern for those kind of exposures as we
20 do for the male exposure?

21 DR. YAO: Right. So I can help answer that
22 question. At least for safety purposes in terms of

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1 topically indicated products, we actually do look at
2 systemic levels in terms of whether or not we believe
3 there could be a potential safety risk, but that's
4 really kind of a separate issue. And I think the point
5 that I heard, and is very well taken, is the issue of -
6 - and, again, I think we are trying to be consistent,
7 too, internally -- which is that a teratogenic risk is
8 a risk like any other risk. I mean, it is a safety
9 risk, it's a safety risk to a specific population, but
10 it is not any different than any other safety risk we
11 might consider. And I think that the point is well
12 taken, and we're going to have to do our homework about
13 that to say, have we even really looked at transmission
14 of semen as producing a side effect in a female partner
15 for any safety risk? And I think that that's what I'm
16 hearing is important to establish before we go running
17 down the track of we think that this is especially
18 important as a teratogenic risk. So thank you for that
19 feedback.

20 DR. WINTERSTEIN: Dr. DiGiovanna.

21 DR. DIGIOVANNA: The only point I wanted to
22 make is it becomes a little more complicated with 13-

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1 cis-retinoic acid, or isotretinoin, because while it
2 was thought to be a synthetic drug when it was
3 developed, it's actually present in almost every cell
4 of the body, if not all of them. So the concentration
5 of it becomes important if it's a component of every
6 cell. So you somehow have to have that in the equation
7 with that drug.

8 DR. WINTERSTEIN: Dr. Wisner?

9 DR. WISNER: So I'm going to ask for some
10 clarification physiologically because I'm really having
11 some difficulty with the biologic plausibility of
12 exposure through semen. So what would happen then is
13 the semen, I'm presuming, would have a concentration
14 physiologically similar to that in the male's
15 bloodstream, so it's not the same as an oral dose, it's
16 a tiny amount, the concentration that would be in his
17 bloodstream, and I don't know of any data to suggest
18 that drugs are concentrated in semen, which then would
19 be distributed into the vagina, and then the way it
20 would get to the fetus would have to be through
21 absorption into the maternal bloodstream. So you've
22 got this tiny amount of drug distributed then through

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1 the woman's entire bloodstream that would be an
2 exposure to the fetus. And I do a lot of work with
3 low-level exposures through breast milk, and this just
4 seems to me to be biologically implausible. We're
5 assuming that the dose is the same as an oral dose, but
6 this is orders of magnitude less.

7 So perhaps if others understand the
8 physiology different than me, this just seems so low on
9 the list of things to be concerned about.

10 DR. WINTERSTEIN: Dr. Hoeger?

11 DR. HOEGER: So I agree. I think, as
12 preface, the biological plausibility is low, but just
13 in reference to this point, clearly there are drugs
14 that could absorb directly into the endometrium at very
15 low serum levels, this is in progesterone specifically,
16 and there is a lot of data on that in reproductive
17 medicine. And there are also drugs that are
18 concentrated in the male reproductive tract. So I
19 think there are some mechanisms by which it could be
20 more concentrated than what you might measure in the
21 woman's serum. But again you have to think about the
22 frequency of exposures, and a single episode of semen

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1 exposure, which may be the only thing we're talking
2 about here, it's not the same as taking a drug over
3 time.

4 DR. WISNER: So could I just ask, you were
5 talking about the endometrium, so is there a mechanism
6 other than through absorption from the vagina that the
7 fetus would be exposed? I mean, there wouldn't be any
8 direct drug travel up into the endometrial tissue.

9 DR. HOEGER: Well, there is with respect to
10 progesterone, but it would still have to cross the
11 placenta.

12 DR. WISNER: In pregnancy?

13 DR. HOEGER: Well, yeah, we use it as
14 pregnancy support, for luteal support.

15 DR. WISNER: Hmm. Okay. I'm sorry, just one
16 final thing. But you're using it as a dose into the
17 vagina that's designed to be a therapeutic dose, not a
18 semen amount that would be equivalent to the low level
19 concentration in the man's semen. I mean, it just
20 seems like orders of magnitude difference to me still.

21 DR. HOEGER: Right. I agree with you. I was
22 just clarifying the point that there are drugs that you

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1 can't measure in the woman's serum.

2 DR. WINTERSTEIN: It seems like there is
3 pharmacologically a way it could happen, and I think
4 that's probably the only thing that's relevant. Okay.

5 Dr. Morrato, and then we move on to Question
6 4.

7 DR. MORRATO: Yeah. I just wanted to comment
8 to the point you had raised earlier, that on one hand
9 this is just a risk and we should manage it like we
10 manage other risks, but I thought it would be useful to
11 note that there is a whole line of literature on risk
12 perception -- right? -- and risks to children, risks to
13 people that are perceived as innocent or not getting
14 the benefit of whatever they're doing and there are
15 kind of unintended risks or actually perceived more
16 highly as being severe, and I think that often is the
17 case with these class of drugs, are these issues as
18 well. I mean, the risk perspective is much higher on
19 the effects of children. And so it's going to be a
20 challenge to try and just say it's like any other risk
21 when I think from a societal perspective, they are
22 perceived differently.

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1 DR. YAO: No doubt.

2 DR. WINTERSTEIN: You got everything you
3 needed, you need; right? You're good?

4 DR. YAO: Yes. Thank you.

5 DR. WINTERSTEIN: Okay. Then we move on to
6 Question Number 4: "In the committee's view, what
7 would be the benefits of implementing a targeted REMS
8 program for a teratogenic drug to specific at-risk
9 populations?" And B: "What are the potential negative
10 consequences of implementing a targeted REMS program
11 for a teratogenic drug to specific at-risk populations?
12 Include in the discussion the feasibility of designing
13 and successfully implementing a targeted risk
14 management program and the potential impact of a
15 targeted program on patients' access to drug and
16 potential burdens to the health care system."

17 So to give us a framework, what we are
18 essentially talking about is that REMS would be
19 targeted, or even restricted, to the at-risk population
20 that we have defined before, in Question Number 2 -- or
21 1 -- no, 2. So rather than involving everybody in a
22 REMS, we would be able to enroll only those patients,

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1 only those women, for example, into a REMS who are of
2 childbearing age, and what would everybody think about
3 approach like that, the advantages and disadvantages of
4 doing so?

5 Dr. Shapiro?

6 DR. SHAPIRO: So wouldn't it depend on what
7 was in the REMS program and what the objective of it
8 was? So, for example, if it was to create a registry
9 so we could get smarter about what happens with these
10 at-risk people, then that might lead to one answer, but
11 if it was to restrict access, it might be another one.
12 Right? I mean, I think we need more information about
13 what kind of REMS program we're talking about.

14 DR. WINTERSTEIN: Okay, so --

15 DR. MANZO: Well, I guess we could take an
16 example, and this could be hypothetical. If you have a
17 risk in females who are of reproductive potential, not
18 so much of a concern males, and so the requirements --
19 that is, required counseling, pregnancy testing --
20 would really only be required of females. Those are
21 the ones, those are the patients, that are at risk for
22 potential fetal exposure. What would be the advantages

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1 of only including that population as opposed to
2 enrolling every patient, which is what's being done for
3 I think probably all of the ETASU REMS, or at least
4 most of the ETASU REMS that have other documentation of
5 safety as conditions, so requirements for pregnancy
6 testing?

7 DR. SHAPIRO: So you're talking about as
8 components of the REMS, counseling, and not just
9 tracking, not just data gathering, not just --

10 DR. MANZO: Correct. Correct.

11 DR. SHAPIRO: Okay.

12 DR. WINTERSTEIN: Dr. DiGiovanna?

13 DR. SLATKO: Just to clarify, so the idea
14 would be to spare -- to reduce the burden and allow
15 access in the population, a subset of the population,
16 who was not at high risk, to just not have the REMS
17 interventions and education and restrictions apply to
18 men and women not of -- females not of reproductive
19 potential because they are at very low risk of
20 experiencing the adverse event. I'm restating the
21 question in the opposite.

22 DR. SHAPIRO: Okay.

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1 DR. WINTERSTEIN: Dr. DiGiovanna?

2 DR. DIGIOVANNA: So the way I would look at
3 this is with respect, for example, to isotretinoin, and
4 I don't know if you are looking only at indicated or
5 off-label indications, but so isotretinoin is indicated
6 for resistant nodulocystic acne, but it's also used in
7 many other situations. So, for example, a not common
8 condition is neuroblastoma, which occurs in children,
9 it's about 7 or 8 percent, I think, of cancers in young
10 children, and it largely, I think about 75 percent,
11 occurs in children under the age of 2, and it's
12 extremely rare as they get older, and very rare
13 apparently over the age of 10, but for high-risk
14 neuroblastoma my understanding is this is part of the
15 therapy. Isotretinoin also is used for people that
16 have less common conditions, but in adults generally
17 who have had severe sun damage and post-transplantation
18 and get lots of skin cancers, it's one of the
19 modalities they use as skin cancer chemo prevention,
20 and for patients that have rare inherited disorders or
21 ichthyoses.

22 So, for example, the REMS program wouldn't be

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1 useful for the 2-year-old with neuroblastoma where
2 there would be a period of treatment. So I think
3 targeting for certain situations for populations makes
4 very much sense, particularly with that drug. I'm not
5 so sure about every drug.

6 DR. WINTERSTEIN: Dr. Chambers?

7 DR. CHAMBERS: I think it makes sense in my
8 view to target to the specific at-risk population as
9 well. It would reduce the burden economically and the
10 burden to males and it may have some potential impact
11 on females' access to the drug, but that's the at-risk
12 population, so I guess that sort of comes with the
13 package, and I don't see any reason not to do it. The
14 only reason I can see not to target a specific
15 population is because of medication sharing.

16 DR. WINTERSTEIN: Dr. Morrato?

17 DR. MORRATO: I agree with the last two
18 comments. As we think of the theoretical at-risk
19 populations, when it's age, when it's sex, those are
20 very concrete and easily discernible, so as long as
21 we're not thinking of at-risk populations that are
22 outside of those kinds of demographic parameters, I

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1 don't know if that's what FDA was envisioning, that
2 there might be other groups based on behaviors or
3 settings, for example, then I hope to see some really
4 good diagnostic validity of the ability of people to
5 identify with certain sensitivity, specificity,
6 positive predictive value, et cetera, those at-risk
7 groups such that you're not making things more gray and
8 complicated than was the intention, I think. But I
9 don't know if that's what FDA is conceiving when they
10 think of at-risk groups or if it's simply things like
11 age demographic.

12 DR. WINTERSTEIN: Dr. Woods?

13 DR. WOODS: Just as point of clarification,
14 there is good precedent for identifying at-risk
15 patients for REMS; correct? I mean, I think of the ESA
16 program. Not being completely familiar with all of the
17 REMS programs, I mean, there is good precedent for
18 this, and could you maybe tell us a little bit about
19 what has been tried and true and how you've developed
20 that in other areas?

21 DR. MANZO: So we do have an ESA REMS that's
22 different depending upon the population that's being

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1 treated, so the restrictions really only apply to the
2 oncology patients. I think those are a little bit
3 easier to identify because it's primarily used either
4 for the oncology indications or for patients that have
5 renal dysfunction, and dosing regimens are entirely
6 different for those. And there isn't really a patient
7 enrollment component to that either, so it's not as
8 though they have to sort of gate out. They can gate
9 out various patients. Really the requirements apply
10 primarily to the health care providers that are
11 prescribing and dispensing the drugs.

12 For these REMS with ETASU, we really are
13 talking about patient enrollment, enrollment of every
14 patient that's taking the drug, and to some extent this
15 has been done because of what was already discussed,
16 really sensitivity around classifying patients,
17 appropriately classifying patients, in the appropriate
18 category, risk category, and also having a feasible way
19 to really sort of track or ensure there is no, on the
20 back end, you know, at the pharmacy level, no way for
21 those pharmacies to really be able to identify the at-
22 risk population. So which patients should be part of

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1 the program versus those that shouldn't? Particularly
2 difficult I think in females, they're not obviously
3 going to know which ones are females of childbearing
4 potential. And there is some concern also with
5 medication sharing. We have some evidence that there
6 has been some sharing in various programs.

7 DR. WINTERSTEIN: Dr. Francis?

8 DR. FRANCIS: Yeah, I'm just wondering, would
9 there be a way to tie the REMS into providing an
10 incentive to get research done to answer some of these
11 questions? And the issue of sort of having either an
12 expiration date or at some point in the future taking
13 an evaluation of how effective a REMS was has come up a
14 number of times, and I'm just wondering if there is a
15 way where you could implement a particular REMS with
16 the idea that once data was submitted by the sponsor,
17 that an evaluation would be conducted, and then given
18 the results of that, modifications would be made.

19 And I've also been looking on PubMed, and
20 apparently there are some data in rodent models about
21 male-mediated developmental toxicity, and
22 cyclophosphamide is one of the ones that keeps coming

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1 up all the time, but, just as everybody else has said,
2 there does not seem to be any reports of actual studies
3 that have been done and confirmed in humans.

4 DR. WINTERSTEIN: Dr. Conover?

5 MS. CONOVER: I have mixed feelings about
6 targeting it to at-risk because I am concerned about
7 the burden on people that are unlikely to become
8 pregnant, but on the other hand, there may be 10
9 Accutane exposures in pregnancy that I have seen at the
10 Nebraska Teratogen Service. Two of them were due to
11 sharing, it was the man in the couple that was
12 prescribed the medication, not the woman, but he shared
13 with her. And a third one was in someone who was
14 determined to be too young to be pregnant and got
15 pregnant.

16 So I think that in actual practice defining
17 whether you're menopausal and also whether you're
18 pubertal, I mean, we can define it clinically or we can
19 define it technically here, but clinically, I think
20 that proof of those things is slippery in actual day-
21 to-day practice.

22 DR. WINTERSTEIN: Dr. Liebmann?

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1 DR. LIEBMANN: So I can certainly appreciate
2 where a drug like isotretinoin would be and could be
3 problematic with sharing. The drugs that I personally
4 use in my patients, lenalidomide and thalidomide, for
5 myeloma, where the median age of onset of that disease
6 is about 68 or 69, most of my patients are good sports
7 and they listen to the whole spiel about don't get
8 pregnant with a certain bemused detachment.

9 (Laughter.)

10 DR. LIEBMANN: But, you know, for some of
11 them it is, why are you making me fill out one more
12 form? And needless to say, then there is a certain
13 amount of staff involvement and recordkeeping and all
14 that. We have already heard how up till now there has
15 been tremendous discretion in how REMS has been
16 applied. So the Sonic hedgehog inhibitor, which should
17 do horrible things to the fetus, is not under a REMS
18 program with, I think, good reason, because it's a
19 limited patient population who will be on it for a very
20 limited period of time and who also probably are
21 generally elderly. So I don't see why judgment couldn't
22 also be applied to selecting out at-risk populations

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1 based on the drug, based on the indications, you know,
2 based on the population that's going to be receiving
3 it.

4 DR. WINTERSTEIN: All right. I think that
5 summarizes it nicely, so I will just repeat what you
6 just said more or less. It seems that the panel
7 appreciates the idea of reducing the burden in
8 particular for populations who are clearly not at risk.
9 The panel sees sharing as one of the greatest
10 disadvantages, or the risk for sharing as one of the
11 greatest disadvantages, and focusing on a population at
12 risk. And that, of course, suggests that depending on
13 the medication as well as the target population, that
14 risk of sharing may need to be evaluated, and it might
15 turn out very differently, and therefore the decision
16 might be tailored to the particular drug and the
17 particular population that is focused on with the
18 indication.

19 Yes, please.

20 DR. KASHOKI: If you don't mind, if you could
21 spend some minutes just talking about the issues that
22 are raised in the second part of the question, which is

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1 the feasibility of doing this. There would have to be
2 some kind of process involved in terms of how do we
3 actually identify and make sure we've got the right
4 people, and who is going to have to do it, and where
5 this would have to occur. So by saying, yes, we should
6 target, there are some consequences, I guess, to that,
7 and we would like for people to spend some time
8 discussing what you think would be involved in that and
9 whether then that changes your mind about, yes, we
10 should target.

11 DR. WINTERSTEIN: Mm-hmm. Before I lose my
12 last thought, which actually responds to this part to a
13 certain degree, was Dr. Morrato's comment to try to
14 establish good diagnostic validity for whatever
15 identification method would be used and that the
16 criteria that would be used should be objective and
17 should not focus on certain behaviors or assumed
18 behaviors or specific settings, but, rather, objective
19 criteria like gender and age and perhaps certain
20 indications and so forth, but maybe we can spend some
21 more time on the feasibility question.

22 When you're asking about feasibility, just

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1 given what I just said, are you also thinking about how
2 exactly that really would be implemented in practice?
3 Is that where you're getting at?

4 DR. MANZO: Well, you can imagine, I mean, if
5 you had a program that only required enrollment of
6 females of reproductive potential, so the alternative
7 is that you don't have to enroll those that aren't. So
8 would there be a risk of taking sort of the easy road
9 if not enrolling patients and misclassifying them
10 because it's easier to get the drug?

11 DR. WINTERSTEIN: Dr. Fingert?

12 DR. FINGERT: So, Dr. Kashoki, to try to
13 address your question, I think I would like to point
14 out something again, that when we're talking about
15 burden and the balance of burden and how to implement a
16 targeted program, what I've heard so far today is some
17 examples of burden. Dr. Liebmann talked about form
18 completion as a burden, and in the briefing document it
19 talks about shipment delays as a burden. And again,
20 similar to what I said before, there is, in my mind,
21 sort of a bias here of where our eyes are. Our eyes
22 are on products that are being successfully shipped and

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1 programs that have successfully been supported by
2 sponsors to move forward and to become marketed. The
3 ones that dropped out because the burdens were so high
4 we're not talking about, they're not in our purview.

5 My point on this is I think I want to get
6 back to something that was said this morning, that
7 having other stakeholders address this question I think
8 would be important, to try to find a way to bring in
9 people who are not here at the table who can talk about
10 more than just shipment delays. I mean, my thinking is
11 that even if we solve the form completion or the
12 shipment delay problem, we really haven't totally
13 addressed the balance of dealing with the multiple
14 burdens, we haven't really even understood the multiple
15 burdens that are out there with these programs and how
16 they should be maybe addressed more innovatively by the
17 stakeholders in collaboration with the Agency.

18 And, again, I point to the fact that there
19 was a very interesting white paper by the American
20 Pharmacy Association about REMS, and they had some
21 very, I thought, novel ideas about like pilot programs
22 as a way to stage in certain types of targeted programs

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1 we haven't even talked about, and I'm not part of the
2 American Pharmacy Association, but there are groups out
3 there who put a lot of thought and effort into this and
4 really do care about it, and they're just not here at
5 this table.

6 DR. WINTERSTEIN: Just to focus back on the
7 discussion at hand, I think what our charge was more or
8 less was to talk about whether we could see a program
9 that providers, either pharmacists or physicians, would
10 be asked to identify who was the at-risk population,
11 whether we would see that work, whether we would see
12 that as a feasible way forward, and basically easing
13 the risk for those the providers would identify as not
14 being at risk.

15 I saw a few hands coming up.

16 Dr. DiGiovanna?

17 DR. DIGIOVANNA: So you asked about how one
18 would think about designing a program that would target
19 specific populations. So the one that I would be
20 familiar with would be isotretinoin, and we've heard
21 that maybe there were anecdotally two or three cases
22 where if, for example, a not at-risk population,

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1 presumably males, who should be fairly easy to
2 identify, the risk would be their sharing of the drug.

3 So there is a registry. That information
4 should be available, of the pregnancies that have
5 occurred in that situation. And if they are below the
6 risk of failure rate of contraception or below the risk
7 of the background teratogenicity rate in the
8 population, then perhaps that isn't a real risk that
9 exists and perhaps that would be a good way to go or a
10 safe way to go. So I would think perhaps that
11 information may already be available or could easily be
12 identified because there is a registry.

13 So, again, identifying the actual number of
14 cases that have been attributed to sharing of
15 medication where there has been a pregnancy and to see
16 if there has ever been an adverse event in those
17 pregnancies, and if it reaches the level of the
18 background population, then perhaps that could be a
19 plausible risk, but if it's not, it would be hard to
20 justify that it's even a plausible risk, and I would
21 think that would be a safe population, easy to
22 identify, to be able test whether this selected

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1 population, at-risk females of childbearing potential,
2 would be a way to limit and reduce the burden.

3 DR. WINTERSTEIN: Dr. Kaboli?

4 DR. KABOLI: Yeah. I think this discussion
5 is actually pointing out nicely why it needs to be a
6 targeted program. This is risk mitigation, not risk
7 elimination. For example, if there was a drug that was
8 only given in an infusion center intravenously, there
9 is no way that can be shared, so we don't worry about
10 either sharing or drug diversion, but if there are
11 other drugs, like isotretinoin, that really has a real
12 potential in young people to be shared because somebody
13 thinks they've got bad acne and they get the drug from
14 their friends, totally different drug.

15 So, again, I think going with the targeted
16 thing makes so much sense. I mean, to me that's what
17 this discussion is leading towards, to answer Question
18 A in 4, A and B.

19 DR. WINTERSTEIN: And if there were C, which
20 is that last paragraph about feasibility, I'll try one
21 more time.

22 (Laughter.)

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1 DR. WINTERSTEIN: That would be, so do we
2 think that feasibly it would be possible to have
3 providers identify the at-risk population, and what
4 would be the concerns about doing so? Did I phrase
5 your question correctly?

6 (No audible response.)

7 DR. WINTERSTEIN: Okay. Any thoughts?
8 Dr. Cragan?

9 DR. CRAGAN: I just wanted to say I come back
10 again to the level of risk that is there, and so for
11 isotretinoin, the level of fetal risk is so high with
12 that drug that that might be a particular situation
13 where you would think about, because of the risk of
14 medication sharing, going wider than just the at-risk
15 population. In general, I totally agree with the at-
16 risk population, but maybe it's a place where the
17 strength, the level of risk, is something you would
18 take into account when there is a concern about
19 medication sharing and look at going wider in those
20 circumstances.

21 DR. WINTERSTEIN: All right.

22 Dr. Liebmann?

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1 DR. LIEBMANN: I guess since you put the
2 question out there, I almost feel obligated to respond
3 to it.

4 DR. WINTERSTEIN: Thank you.

5 (Laughter.)

6 DR. LIEBMANN: So to my mind, the answer is
7 that, yes, physicians do risk assessment all the time.
8 So in the world of oncology, we do risk
9 assessment on: How bad is the tumor? Does it rise to
10 the need for adjuvant chemotherapy, for example? Does
11 the patient's heart function merit the administration
12 of doxorubicin or trastuzumab? You know, these are
13 conscious decisions that are made all the time without
14 the need for any forms or regulatory oversight, it's
15 part of the practice of medicine.

16 I think for drugs like we're talking here
17 that have a big flashing neon black box around them
18 that bad things can happen if pregnant women are
19 exposed to them, it's actually a little bit hard for me
20 to imagine that capable physicians wouldn't risk
21 manage.

22 DR. WINTERSTEIN: What came to my mind, just

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1 to add to this discussion, was the earlier presentation
2 during the public comment period where it appears that
3 providers circumvent the original idea of a REMS by
4 prescribing the generic ingredients of the combination
5 drugs separately so that the whole REMS involvement
6 phase is circumvented. So here is an example where at
7 least the intent of the REMS is not acknowledged by the
8 prescriber perhaps because the risk is understood to be
9 low, but that would be the counterbalance. I think
10 that would be an example that I assume the FDA has in
11 mind where if there was concern to leave that
12 responsibility with the provider.

13 Dr. Madigan?

14 DR. MADIGAN: Just a quick comment. I assume
15 we're not talking about identifying women of
16 childbearing risk as being at risk and not other women
17 in this regard, because if so, who makes the call? Or
18 are we? Is that on the table as one of the potentially
19 at-risk populations that would be targeted?

20 DR. TASSINARI: It would be nice for you to
21 expand on that, please.

22 DR. MADIGAN: I'm just saying, so if one were

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1 to define the at-risk population as women of
2 childbearing risk and then apply REMS to that
3 population and not to women not of childbearing age,
4 then who decides? Like it's one thing to target
5 females and not males, that's pretty straightforward, I
6 guess, but women of childbearing age is a different
7 matter, it seems to me. There are boundary cases.

8 DR. WINTERSTEIN: Which brings us back to the
9 diagnostic validity it appears. Yeah.

10 Dr. Fingert?

11 DR. FINGERT: So the comment made earlier
12 about the example where someone took a drug as an
13 individual drug that's indicated -- prescribed for
14 epilepsy and used it for weight loss is really off-
15 label use, and the medication sharing can be viewed in
16 a way of off-label use.

17 So the way I view this question, it kind of
18 gets to having some advice here that we can provide
19 about how to manage off-label use as a broader
20 category.

21 And Dr. Liemann's comment earlier, I think he
22 was getting to the issue that oncology has been very

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1 vocal about their capacity as prescribers to have the
2 prescriber profile and control and educate themselves
3 about the drug. But I would like to ask the question I
4 think the Agency would like to hear, I think, how this
5 applies for other examples besides oncology to avoid
6 off-label use. I mean, does it apply -- for example,
7 we talked earlier today about the example of someone in
8 deep depression who was going to commit suicide if they
9 didn't get a drug even though they might have the risk
10 of pregnancy, well, would that be managed by a
11 specialist? Are there other examples where the
12 specialty kind of prescribing could help in this
13 implementation of a targeted risk management approach
14 besides what we heard about oncology?

15 DR. WINTERSTEIN: Well, it appears that the
16 answer is again it depends. From what I sense from the
17 committee, it seems that there may be targeted
18 medications where it would make a lot of sense and
19 there would be very limited risk to leave it to the
20 provider to diagnose who was at risk, and I think a
21 good example is oncology medication that is used in 65-
22 year-olds. And then there may be some instances where

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1 there may be, a greater potential for sharing, but also
2 perhaps a greater potential for not really recognizing
3 the risk of the medication appropriately where a focus
4 on an adverse population may be complicated or
5 problematic. I think that summarizes the views of the
6 committee?

7 (No audible response.)

8 DR. WINTERSTEIN: Excellent. Good.

9 Yes?

10 DR. CHAMBERS: I think it's also important to
11 state that it doesn't have to be one or the other, so
12 it could be kind of a hybrid design where sort of
13 information was provided to all who were being
14 prescribed, but the targeted population for the more
15 proactive REMS intervention would be women of
16 childbearing potential.

17 DR. WINTERSTEIN: Thank you, Dr. Chambers.
18 Yeah, so there could be different levels of a REMS for
19 different populations. Right. Yeah.

20 DR. TASSINARI: I'm sorry to keep this going,
21 but just for final clarity, can you articulate again
22 what the sense of the committee is around whether or

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1 not providers can reliably identify the targeted
2 population should you have a targeted REMS? I'm not
3 sure I really understand what the sense of the
4 committee is on that.

5 DR. WINTERSTEIN: I heard that there are
6 certainly -- I heard from Dr. Liebmann, if I remember
7 this correctly, he described a scenario if there were a
8 very significant severe risk that a provider would be
9 very aware of, that he would expect that a provider
10 would reliably identify the population at risk.

11 So there were a few limitations put around
12 this particular statement, and me, as part of the
13 committee, quoted an example where it appears that
14 there are prescribers who certainly have circumvented a
15 REMS according to the public statement that we heard
16 earlier, which would give the other side of that
17 scenario. I think that summarizes what I heard from
18 the committee. Were there any other comments?

19 Dr. DiGiovanna?

20 DR. DIGIOVANNA: I think the other dimension
21 to this is it depends on how you define it. I mean, if
22 it's men or women, that's pretty easy, but if you're

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1 going to define it as a female of childbearing
2 potential, then that may be quite nebulous and it may
3 actually change over time, over decades. So I think it
4 really depends on what the population is whether or not
5 the providers will be able to reliably characterize
6 them. And often that's part of the definition I think
7 you've asked for.

8 DR. WINTERSTEIN: Dr. Kaboli.

9 DR. KABOLI: And I also think it depends on
10 how you set up a system. I mean, you set up a system
11 that facilitates people doing the right thing. And the
12 example is with your ATM card, some ATMs are designed
13 that you have to put your PIN number in and then it
14 gives you your card back, so that you take your card
15 before it gives you the money. Otherwise, I'm sure I'm
16 not the only idiot here who has walked away from the
17 ATM machine and left my card in there because the
18 system was designed in a way that made me fail.

19 So I think the same thing with these type
20 systems, is that you can design a system that allows
21 people to get to the right decision point to say,
22 "Okay, no, this patient doesn't need it," and therefore

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1 they fall out, and that's appropriate. I mean, if it's
2 just an optional thing, of course. If it's optional
3 for me, I'm not going to do it, you know, you have to
4 make it easy for me to do the right thing.

5 DR. WINTERSTEIN: Dr. Woods?

6 DR. WOODS: I'll answer that in a little bit
7 different way, but based on experience from the ground
8 level, it is a challenge based on our experience with
9 the ESA program. And it's particularly difficult as
10 patients move across lines of care to know who has and
11 who hasn't been appropriately counseled or whatever.

12 DR. WINTERSTEIN: Just to clarify, this is
13 the criterion that there needs to be a certain
14 hematocrit or hemoglobin or whatever; right? So there
15 was a specific lab value that --

16 DR. WOODS: Knowing whether the patient is
17 receiving an ESA for an oncology-related indication or
18 some other indication. So it's a challenge.

19 DR. WINTERSTEIN: Okay. So to summarize
20 this, it seems that we feel that it is possible to
21 reliably identify gender, but as we move down to any
22 other criteria, things might become a little bit more

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1 tricky.

2 Dr. Fingert, anything related to that, or can
3 we move on?

4 DR. FINGERT: Just before we get too far
5 away, Dr. DiGiovanna just presented a concept of
6 male/female identifiable, but maybe an all-female
7 program would not, and therefore you might need a REMS.
8 I just want to say that that is somewhat speculative,
9 and I would ask the Agency if, in that kind of
10 situation, a sponsor were to do a nonintervention kind
11 of epidemiologic study, a survey, among prescribers, to
12 see, to get actual evidence, and not speculate, to get
13 evidence, that they can identify an at-risk population,
14 that the prescribers do, do that, that they understand
15 if there are females in their practices or not, would
16 that kind of thing help in the collaborative
17 development of the right kind of focused REMS?

18 DR. KASHOKI: Yes.

19 DR. WINTERSTEIN: All right. Moving on to
20 Question 5, "Occasionally the same teratogenic drug may
21 be used for different treatment indications. Provide
22 your recommendation as to whether or not a consistent

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1 risk management approach should be employed for a
2 teratogenic drug irrespective of whether it is used to
3 treat different medical conditions.

4 Discuss the following factors that might
5 influence your decision and their relative importance
6 for such a decision: the medical condition being
7 treated, the characteristics of the patient population
8 likely to use it, the familiarity of the various
9 prescriber types with preventing, identifying, and
10 monitoring for teratogenic effects, and the presence of
11 existing pregnancy prevention and/or monitoring
12 safeguards within the expected treatment setting."

13 Dr. Shapiro?

14 DR. SHAPIRO: This is what I was talking
15 about before a little bit, and I definitely think that
16 there should be differences based on some of these and
17 some other factors and that, for example, if we kind of
18 try to set up the paradigm for the objective of the
19 REMS, which is to enhance safety but acknowledge the
20 limitations posed on autonomy or access and the burden
21 on the health care system, it is more justifiable to do
22 that when the medical condition being treated is more

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1 serious, I mean, it is less justifiable to do that,
2 that is, we want to make it easier for everybody to get
3 access to that drug, I think, when the drug is treating
4 a more serious condition. So I'm not the expert about
5 rank ordering what's more serious, but that's how I
6 would approach, for example, 5A.

7 And going to B, to the extent that the risk
8 is enhanced because of the greater likelihood of
9 sharing or off-label indications, then I think that
10 would justify again more restriction and more burden,
11 i.e., a more rigorous REMS, because you need it more.

12 DR. WINTERSTEIN: I'm waiting for Dr. Morrato
13 to respond to this. I'm hearing you mumbling already,
14 so go ahead.

15 (Laughter.)

16 DR. MORRATO: No, I'm just curious. I'm just
17 trying to make sure I understand the reasoning. So how
18 would you address the fact that it's the same drug with
19 the same risk, and if the goal is to mitigate that
20 risk, now we're using different methods depending upon
21 the perceived value of use of that drug for a different
22 group of patients?

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1 DR. SHAPIRO: It's the same risk to the fetus
2 --

3 DR. MORRATO: Right.

4 DR. SHAPIRO: -- but it's of different
5 benefit to the woman. And I don't know how you can not
6 factor that in.

7 DR. MORRATO: So if it has greater benefit to
8 the woman, then we will do less presumably to mitigate
9 the risk?

10 DR. SHAPIRO: That's where I come out, yeah.

11 DR. MORRATO: Okay. I mean, for me
12 personally, I see it more on you're trying to deal with
13 the absolute risk, and that that benefit to woman comes
14 more into the decision of whether or not to approve the
15 drug as opposed to, how do I think about mitigating the
16 risk? So if it's meta-threshold that I say I want to
17 mitigate this risk, then I'm more hesitant to say we do
18 different approaches by different indications --

19 DR. SHAPIRO: And I do, and I think that's
20 why that makes this such an interesting conversation.

21 DR. MORRATO: Right, no, yeah. I'm just kind
22 of -- I'm not trying to change your view, I'm just kind

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1 of sharing my thinking because I think that's what
2 leads to the problem that we heard in the public forum
3 where you have folks gaming the system to get drugs,
4 the same drug, from a different venue in order to
5 either get it -- in this case, it may also be price
6 because it's generic Topamax, I believe, versus a
7 brand-new drug, but it also has different REMS, and so
8 it's hard to communicate then -- and it also leads to a
9 value statement in this case. All right. The person
10 that has seizures, how do I value the benefit of a
11 seizure medication for you versus someone that has
12 weight loss and is obese; right?

13 And so we had actually in the case of the
14 obesity drugs, we had public comment to say, "You're
15 stigmatizing me, why do I have to go under a more
16 rigorous system compared to someone else? Is it
17 because I'm a disadvantaged population," et cetera. So
18 I see where you're going, but I think it makes it kind
19 of hard to implement --

20 DR. SHAPIRO: Well, and I should say that I
21 don't think that these are all the factors. I mean, I
22 think that your understanding -- and I certainly

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1 understand and appreciate your point of view, too. So,
2 for example, obesity versus seizures, if there are
3 another factor that would factor into my approach would
4 be, are there alternatives? So if this is a horrible
5 condition for this woman and there is really no
6 alternatives for that condition, that would be even
7 more important to me in my paradigm.

8 DR. MORRATO: If you had fewer options, then
9 I would want to make my barriers lower. Is that what
10 you're saying then, too?

11 DR. SHAPIRO: Yes. That's right.

12 DR. MORRATO: Because the perceived benefit
13 would be higher.

14 DR. SHAPIRO: Fewer options, bigger problem
15 for the woman's underlying condition.

16 DR. WINTERSTEIN: There are, of course,
17 separate considerations. I mean, one part was the
18 bigger problem or the indication. This did not come up
19 in Question 1 because that would be the same thing. I
20 mean, in Question 1, it seemed that the committee
21 really looked specifically at the risk to the child in
22 order to define the nature of the REMS. What you are

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1 bringing up would actually add the other component back
2 in there.

3 I think the other part that we need to
4 consider in all of this is that burden does not equal
5 access. So access may still be there even though there
6 may be burden, so the critical question that you're
7 raising might be more, do we want to ease the burden
8 for somebody who has a more severe condition than for
9 somebody who has a less severe condition by sacrificing
10 whatever the risk to the fetus is? And so it's not
11 access necessarily, it is really burden, which brings
12 us back to the evaluation of burden and so forth.

13 I think Dr. Rasmussen was next?

14 DR. RASMUSSEN: Yeah, I think I would base it
15 regardless of medical condition. I think I would agree
16 with Dr. Morrato, that to me it's the risk to the
17 fetus, if there is significant risk to the fetus. And
18 otherwise, I think there could be, you know, I mean,
19 physicians saying, "Oh, I don't want to go through all
20 this hassle, I'm just going to check that I prescribed
21 this for seizures, not for obesity," or whatever. I
22 just think it would be really complicated to have a

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1 different for different medical conditions.

2 DR. WINTERSTEIN: Dr. Madigan?

3 DR. MADIGAN: I just want to echo your point
4 about burden. I mean, so if you had a drug that was
5 used to treat headaches, and it's used to treat cancer,
6 it would seem to be the issue of whether that the --
7 and it poses a birth defect risk -- the issue of
8 whether it should be done under controlled
9 circumstances or prescribed carefully and so on with
10 warnings seems to me has nothing to do with whether
11 it's used for a headache or cancer, but it has -- I'm
12 basically just echoing your point, it has to do with
13 burden. So for a headache, the burden might be too
14 much, so you might not use it, but it would seem to me
15 that given that you're going to use it, we need to put
16 the warnings and controls in place.

17 DR. WINTERSTEIN: Okay. Where is she? There.
18 Ms. Broyles.

19 MS. BROYLES: Hi. I've just tried to put
20 several things in my mind together, but from a patient
21 standpoint, I think I've listened to several things
22 that I can identify with. Certainly, when the patient

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1 is seeing multiple physicians or even just two, and
2 they are actually not their primary physician that
3 prescribes the at-risk drug, and I think if they're a
4 woman in childbearing age, I think when we hear you're
5 at risk if you take this drug, and that person is
6 already on an oral contraceptive, you kind of think,
7 well, then she's covered, but I think with the pharmacy
8 being brought into this has been very helpful because a
9 lot of times if they're the ones prescribing the drug,
10 they can see an interaction, which a lot of times can
11 cause the birth control to be less effective, and the
12 next thing you know, here's a pregnant woman. And so I
13 think those things have been identified here, and I
14 think that's really good.

15 And it certainly goes back to the patient
16 responsibility to get as educated as you can about what
17 you're taking because you can't just expect everybody
18 that's taking care of you to know for you, and there is
19 a lot more information out now than there was 20 years
20 ago when I had a child taking antiseizure medicine, so
21 I'm impressed with that, but I do think there has been
22 a lot of strides, but we can't emphasize enough to know

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1 as much as you can yourself. But the drug
2 interactions, if you add another drug, it changes
3 everything.

4 DR. WINTERSTEIN: Dr. Hoeger?

5 DR. HOEGER: So I have a question about the
6 approval process. There are drugs that are approved
7 for use in men only, such as for prostate cancer, that
8 are now crossing over, and they probably wouldn't have
9 gone through the REMS? Or do they, even if it's not
10 seeking approval for use in women?

11 DR. MANZO: I think much of it depends upon -
12 - some of it may depend upon how it's likely to be used
13 once it's approved. So, I mean, even in the case of
14 vismodegib, for instance, I mean, the thought was that
15 the use in females of reproductive potential would be
16 very low if you have a drug that's only approved for an
17 indication for males, and the likelihood is that it's
18 going to be used only in males, and if we determine
19 that that's not an at-risk population, then it more
20 than likely wouldn't require a REMS to address
21 teratogenicity.

22 DR. HOEGER: So then drugs that cross over,

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1 because there are some that we use in reproductive
2 medicine for hirsutism or alopecia that are only
3 approved for prostate cancer in men, wouldn't have this
4 process, but they are teratogens in women of
5 reproductive age. We use them with contraception, but
6 I don't think there is any process for that.

7 DR. TASSINARI: Well, generally
8 speaking, when a supplemental indication comes through
9 or something crosses over, as you say, when that
10 application comes in, we expect that the study work has
11 been done to expand to that new group, that new
12 indication. So therefore, we would be looking for
13 appropriate clinical trials because we need to know the
14 safety and the efficacy. We may, in certain
15 circumstances and in a circumstance like this where it
16 was reasonable to have only one set of toxicity data,
17 ask for further toxicity data because you're now adding
18 a population that wasn't previously studied. So that's
19 built into the system to make sure that we have the
20 right information to start with to get the scientific
21 evidence and move forward. And then as Dr. Manzo
22 articulated, then we can make these decisions around

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1 REMS.

2 DR. WINTERSTEIN: You know, earlier in
3 Question 1 the panel came up with really the critical
4 view is the absolute risk of the medication, and it
5 seems that the population discussion kind of ties into
6 this, so if there is a population that is expected to
7 have a very small representation of at-risk people in
8 this population, then the absolute risk for birth
9 defects will be very small, which, of course, then
10 would propose that the REMS could be simpler or not as
11 restrictive. I think that's kind of where we are
12 getting. I think it's the continuum of our response to
13 Question 1 that would apply here, I would think.

14 Go ahead. Is it directly related?

15 DR. CHAMBERS: But it seems to me, once
16 you've selected something as being eligible for a REMS
17 for one indication, that it makes sense to have it be
18 uniform across all indications or off-label use, and in
19 many respects, that simplifies the whole process. So
20 if there is a risk that you deem as essential to
21 address, then it should be addressed across all
22 indications. That makes sense to me. It's like

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1 mycophenolate mofetil might be used for one indication
2 more frequently than others, but it makes sense to have
3 a REMS in place for all indications.

4 DR. WINTERSTEIN: Definitely from a practical
5 standpoint probably.

6 Dr. Polifka, and then Dr. Greene.

7 DR. POLIFKA: I don't know if I was
8 misunderstanding the question, but wouldn't dose be an
9 important factor? With methotrexate, for example, low-
10 dose methotrexate doesn't seem to be associated with a
11 risk yet that we've been able to find, but high-dose
12 is. So you might want to change the risk management
13 approach depending on dose. I know that most agents we
14 don't have that kind of information, but --

15 DR. CHAMBERS: And to add to what Janine
16 said, I also think it's important to realize that a
17 risk management strategy doesn't necessarily mean the
18 drug isn't prescribed in pregnancy. So Paxil or
19 valproic acid might need to be prescribed in pregnancy,
20 it doesn't mean that it isn't used, and the same might
21 apply to a dose situation where there was less risk at
22 a certain time in pregnancy or at a certain dose.

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1 UNIDENTIFIED FEMALE SPEAKER: Yeah, that's
2 true.

3 DR. WINTERSTEIN: Dr. Greene?

4 DR. GREENE: I would just like to agree with
5 several other speakers and say that I think that the
6 issue is really the drug in this situation, whether we
7 need to worry about a REMS program or not rather than
8 the condition for which it's being prescribed.

9 I do believe that the reverse will be
10 affected, and that is, whether the presence of a REMS
11 and the degree of burdensomeness of the REMS will
12 affect both provider and patient idea of what they want
13 to get prescribed for a condition, so that if there --
14 and it is rare circumstance that there is only one
15 medication that's available for treating a condition,
16 and I do believe that the presence and the degree of
17 burdensomeness of the REMS will drive prescribing
18 practice rather than think that the condition is going
19 to be an important consideration in whether the
20 medication should be prescribed.

21 DR. WINTERSTEIN: Dr. Whitaker?

22 DR. WHITAKER: I'm just going to respectfully

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1 disagree with that sentiment, and I just wanted to
2 represent the other point of view, that I think the
3 condition is actually extremely important. I think
4 that to divorce this idea of our REMS and ETASU and
5 labeling from access is not right. I mean, I think
6 that it's true that labeling, even strong labels, that
7 REMS all do affect access, and if you implement strict
8 ones on a drug that has benefit for a very severe
9 condition, you are going to affect that condition.

10 So I think that the interplay is a little
11 more subtle, and it's appealing from an implementation
12 point of view, I think, to say we're just going to look
13 at the fetus, but there is not just the fetus involved,
14 there is the woman involved, and she is going to be
15 affected. So I think the condition is really an
16 important factor.

17 And if we had a drug, say, initially that was
18 for headaches, we might have put in a really
19 restrictive REMS with ETASU and require pregnancy
20 tests, et cetera, and then if we discovered it cured
21 cancer, just to go like the absolute opposite
22 direction, we would make that easier to get, I think

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1 certainly, and we would become less concerned about the
2 potential effects on the fetus.

3 And the other time I think when the condition
4 is certainly important in the discussion is when the
5 condition itself can cause fetal effects, and so if we
6 had a great drug for diabetes and we withheld it or had
7 any kind of strong label, any REMS, or REMS with ETASU,
8 that limited access, and then you also have the fetal
9 and maternal effects.

10 DR. GREENE: May I just respond? I would
11 certainly agree with you if it were the case that the
12 drug for which there was a REMS required was unique and
13 the only medication that was efficacious for that very
14 serious condition, but that's rarely the case.

15 DR. WHITAKER: Well, what if it's the best
16 one? I mean, I --

17 DR. GREENE: I think if it is uniquely
18 effective or it is the best drug, it is not going to
19 change prescribing practice. If there are equally
20 efficacious medications available, it will change
21 practice. If it's clearly the best or the only, it's
22 not going to change practice.

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1 DR. WHITAKER: Well, it might not change
2 prescribing practice, it might change compliance from
3 the patient's point of view and/or related things. I
4 just don't know how you can abstract this piece of the
5 equation myself, but --

6 DR. WINTERSTEIN: Dr. Hernandez-Diaz.

7 DR. HERNANDEZ-DIAZ: I agree in principle
8 with doing the REMS based on the risk, not take
9 indication into account, but I think if we look at
10 specific examples, we will not be really following our
11 principle with what we are doing. With some of the
12 examples -- I know we are not supposed to talk about
13 specific examples -- but, for example, with the
14 topiramate, the evidence was coming from the
15 anticonvulsant indication, then we apply the evidence
16 from there to the obesity but apply the REMS only to
17 the obesity and not to the anticonvulsant or migraine
18 indication, and it's not that we are discussing going
19 back and doing a REMS with the anticonvulsant or with
20 other anticonvulsants with probably higher risk. So if
21 we want to follow our principles, we will have to
22 change some of the things we are doing.

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1 DR. WINTERSTEIN: And that was actually one
2 of the issues that had been brought up very early at
3 the discussion of Question Number 1, that whatever
4 framework is developed, it might need to be applied
5 retrospectively to all decisions that have been made in
6 the past, which might, of course, create some work in
7 the long run.

8 Dr. Wisner?

9 DR. WISNER: I've been listening to this
10 discussion, and I'm absolutely fascinated because I'm
11 involved now in a project with our neurologists to look
12 at the circumstances under which anticonvulsants are
13 prescribed to women with epilepsy, and we, of course,
14 probably use even more anticonvulsants to treat women
15 with bipolar disorder, and the thing that concerns me a
16 bit is the assumption that we're making that we know
17 which of these indications are more severe. So we've
18 talked about cancer being more severe. And I would
19 want us to be able to articulate, what does that really
20 mean? Because I work with bariatric surgical patients,
21 women who are obese to the degree that their health is
22 incredibly impaired. So what would the criteria be? I

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1 have patients with migraines where they're basically
2 not functional.

3 So are we talking about the illness being
4 severe, cancer being the "C" word, severe, or are we
5 talking about the impairment in function that results
6 from the disorder? So I wouldn't want to make the
7 assumption that we all know which ones are severe.

8 And just to speak from a mental health
9 standpoint, there are some good studies that show that
10 drugs used to treat mental illnesses are somehow less
11 acceptable, it's a more stigmatized illness. So,
12 again, I would -- I'm not actually sure which side of
13 the debate I come down upon, but that's the one thing I
14 would want to make clear before I would make that
15 decision about which side of the debate to come down
16 upon.

17 DR. WINTERSTEIN: Dr. Liebmann?

18 DR. LIEBMANN: So I agree with the various
19 people who have said that certainly pharmacologically
20 it really doesn't matter the condition that you're
21 using the drug in, the question is: What is the drug?
22 What is the teratogenic risk? And I agree with that

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1 completely.

2 Practically speaking, I'm not sure, in all
3 honesty, how this applies. It seems to me that from
4 the FDA's standpoint, a drug will come to the FDA for
5 an indication, and if it seems to have a significant
6 teratogenic risk, then presumably it would have a REMS
7 applied to it. If subsequently that drug is found to
8 be effective in other indications and people are going
9 to use it off-label, I'm not sure how they're going to
10 get it without going through the REMS. And I must say
11 that practically speaking, in my experience, the
12 biggest roadblock that will be run into is not the REMS
13 but the insurance coverage for the off-label use.

14 So I guess I'm not sure how this applies
15 certainly to a drug that's on patent. For a drug
16 that's generic, I could imagine where this might be a
17 little bit trickier, but just thinking about this, once
18 a drug is approved and it has a REMS applied to it, to
19 my knowledge whether or not you then prescribe that
20 drug for its approved indication or something else,
21 you've still got to go through the REMS to get it.

22 DR. WINTERSTEIN: It's interesting, on that

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1 same note, going back to Question Number 1,
2 theoretically if we follow the notion that it's really
3 the risk that matters and that it's almost impractical
4 to define severity anyways, then with Question Number
5 1, the indication of the drug, in the initial decision
6 whether a REMS should be applied should actually not be
7 a consideration at all because as the drug moves on and
8 experience with the drug moves on, it's very likely
9 that there will be some other indications, either
10 formally approved or in some type of label use, and as
11 said, the practicalities in distinguishing one
12 indication from the other might make it almost
13 impossible to come up with different types of REMS. So
14 going back to Question Number 1, the critical key piece
15 really seems to be the risk and the number of birth
16 defects that would be expected or the actual risk of
17 the medication that is the driver for the REMS.

18 Yeah, Dr. Francis?

19 DR. FRANCIS: Yeah, I mean, clearly today
20 we've been talking about teratogenic risks, but, again,
21 getting back to FDA gets this information in on a
22 particular drug, and, I mean, it's my understanding

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1 they're going to be evaluating all forms of potential
2 toxicity and all sorts of data. So I guess one
3 question that I have, because I think -- and sometimes
4 we've been talking about this as sort of like you
5 either have a REMS related to the teratogenic effects
6 or you don't, but aren't there times when there will be
7 a REMS because of another toxicity? And so wouldn't
8 this just be like perhaps an additional incremental
9 thing that needs to be put into place, but there is
10 already something else that's being of concern? I know
11 earlier there was a drug that they talked about that
12 also had one based upon hepatotoxicity which was
13 evaluated and then removed.

14 So how frequently is the teratogenic effects
15 the driver for these, I mean, where it's like the only
16 one as opposed to one bundled up with others?

17 DR. YAO: So just some points for reminder
18 and clarification. I'll probably come back to repeat
19 Part 2 of the question because we were formulating the
20 answer to Part 1.

21 So to back up to the very start of our
22 conversation, which was the framework, and it's stated

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1 in the background document as well, the vast majority,
2 99 point whatever percent of products with teratogenic
3 risk do not have a REMS, there are only about 9
4 products that do. So the intent of the framework is
5 not to say here is how we're going to explain why we
6 arrived at a decision for a REMS for a teratogen, it's
7 really to ensure that we have a consistent approach to
8 our decision-making about what is the appropriate
9 strategy for a particular drug.

10 Now, we do consider the need for a REMS based
11 on all of the available risk information, and so the
12 REMS is designed to address the serious risks that we
13 feel that in the presence of the program, the benefits
14 of the drug would outweigh the risks. If
15 teratogenicity is one of those serious concerns for
16 which we think a program is necessary to ensure the
17 benefits outweigh the risks, then the REMS would
18 include some kind of components or whatever it might be
19 to address specifically the teratogenic risk.

20 Would management of teratogenicity be an
21 automatic add-on, for example, if there was a product
22 that already was going to have a REMS for another

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1 serious risk? It's not an automatic thing. We would
2 have to be looking at that risk to see, is it necessary
3 to include components of whatever strategy that we're
4 employing as part of the REMS and part of the -- yeah,
5 as part of the REMS.

6 So it facilitates definitely if we are
7 thinking about a REMS for teratogenic risk, if there is
8 already going to be some kind of program in place, then
9 we try and make sure that the combined efforts under
10 the program aren't unduly burdensome, et cetera, and
11 get us what we need. So it facilitates getting there,
12 but it's not necessarily an automatic that if there is
13 a REMS for another reason and there is also
14 teratogenic, we're going to tack that on.

15 Did that answer your question?

16 DR. FRANCIS: Well, but I think the last part
17 of my question was, how often is it the only one, is it
18 the only endpoint of concern, that would drive a REMS?
19 I mean, do you have any examples of the ones that -- I
20 mean --

21 DR. YAO: Thus far, I guess the only thing I
22 can say is that we have nine approved REMS for

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1 teratogens, so nine occasions we've employed a REMS for
2 a teratogen.

3 DR. WINTERSTEIN: Just one announcement. Dr.
4 Wolf had to leave us, so he's no longer on the call. I
5 know that you all have probably not thought about him
6 for a while, but --

7 (Laughter.)

8 DR. WINTERSTEIN: Dr. Morrato.

9 DR. MORRATO: Yeah, I can share one example,
10 and this discussion has really gotten me thinking a
11 bit, and it's somewhat related. There was a review for
12 the drug Truvada, which is a component of the triple
13 cocktail used to treat HIV, and it was coming up for a
14 preventive indication such that you would take this and
15 it would give the patient therefore some power to avoid
16 getting HIV infection, and the discussion was very much
17 like we've been going around except it netted out in a
18 different way, of not having a REMS.

19 In this case, it's similar to the teratogenic
20 risk, and you're both looking at sexual behavior,
21 right? So the concern was that if you misuse the drug
22 and not use safe sex practices, et cetera, you might

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1 therefore have HIV transmission, people would remain on
2 the drug inappropriately, and that would increase risk
3 of HIV resistance development, which would therefore
4 make these therapies not effective anymore.

5 So again it was weighing the benefit of the
6 individual preventing HIV with the risk to others -- in
7 this case, the community, the society -- we're talking
8 about a baby, but it's very similar in how they were
9 weighing the burden of the risk to the individual
10 versus the intended benefit and all of that.

11 So there are examples. And it would have
12 been nice to have had more of an ethical kind of
13 discussion around it because we weren't able to tease
14 out that this is really how people were weighing it
15 because it netted out as a decision that was the
16 beneficence of the patient, and the individual
17 outweighed the risk of the future. Now, that may turn
18 out that if they don't do a REMS or have that, then
19 they're going to have a problem down the road, but
20 that's how kind of the debate weighed out.

21 And so it's very interesting in light of
22 this. So it's not quite teratogenic, but it's a similar

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1 kind of, I guess, context or kind of question I thought
2 I'd share.

3 DR. WINTERSTEIN: All right. To summarize
4 our discussion, there was some controversy that I think
5 was driven by the desire to ease access for patients
6 who suffer severe conditions and to simplify their
7 lives and having less restricted REMS. On the other
8 hand, though, there were several panel members who felt
9 that the risk of the drug remains the same, and that
10 seems to be the only common thing that can be measured
11 reliably across various indications.

12 There were concerns about the practicalities
13 in defining what would be a severe condition or not,
14 and that, of course, would be even more complicated if
15 we are moving into off-label use of medications, so the
16 practicalities and the same issues that we discussed
17 with defining populations at risk, of course, would be
18 potentiated if we talk about the practicalities in
19 defining a certain indication that would then justify
20 one REMS or the other. So I think all the concerns
21 that we had about providers being able to reliably
22 identify a population at risk of course apply here as

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1 well.

2 So my sense was that the majority, but not
3 unambiguously, the panel felt that focusing on specific
4 indications or having REMS focus on specific
5 indications or tailoring the REMS to specific
6 indications may not be a feasible way to go.

7 Do I summarize this appropriately?

8 (No audible response.)

9 DR. WINTERSTEIN: Okay. Dr. Fingert.

10 DR. FINGERT: Well, I do have to say, I don't
11 know if your conclusion about the majority of the panel
12 really reflects data or speculation by those who spoke
13 about it. I mean, I, for one -- if I can be counted in
14 as part of that decision about what the majority said
15 or didn't say -- I do think that there are certainly
16 situations we would want to preserve where the context
17 of care is important.

18 The FDA's briefing document I actually
19 thought was quite good. On page 29 in the framework
20 they talk about clinical use-related factors and
21 context of care, and then page 35, they give some
22 specifics behind it, the prescriber profile and the

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1 clinical setting of use where you have, for instance,
2 frequent physician visits. I mean, certainly there is
3 a difference in my mind between a lifestyle kind of use
4 of a product where you might have the patient see the
5 nurse practitioner for a refill every 3 to 6 months
6 versus one of these more severe kinds of conditions
7 where the physician really needs to see the patient
8 every 3 to 4 weeks or 3 to 4 days depending on how
9 severe the condition is, and so, again, I'm getting to
10 the point that I think there really should be some
11 consideration for preserving that kind of segmentation
12 of whether or not you need the more severe kind of REMS
13 in the lifestyle kind of program versus even if the
14 same use of the drug is used by other prescribers or
15 other context of use.

16 DR. WINTERSTEIN: Any other comments?

17 Yes, please.

18 DR. YAO: Yeah. If I could ask or get
19 clarification from the committee regarding the
20 individual components of this question. So what we
21 believe we heard overall is that for many people the
22 risk is the risk and that that sort of is difficult

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1 then to modify based on a specific condition or
2 another. And so we take that to mean that that would
3 be true regardless of whatever different situations we
4 put up A through D, that the risk is the risk. Is that
5 clear from those who said risk is risk?

6 (No audible response.)

7 DR. YAO: Okay. But I also heard -- yeah.

8 DR. SHAPIRO: I thought the comment was you
9 heard that from the people who talked and then you
10 heard a different point of view, and I don't know --

11 DR. YAO: Yeah, right. So I haven't gotten
12 to that part.

13 DR. SHAPIRO: -- if it's the majority or most
14 or --

15 DR. YAO: Well, yeah, thank you. But I
16 haven't gotten quite there.

17 DR. WINTERSTEIN: I'll revise my statement.
18 The majority of the people who voiced their opinion.
19 Okay.

20 DR. YAO: And I'll just say for the folks who
21 said that risk is risk. But I also heard that there
22 are also people at the table who said, well, I think

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1 you have to take it in the context of the condition and
2 that it's hard to separate, and for those folks, it
3 would be helpful for us to know how these different A
4 through D make a difference to you, and if those of you
5 who believe there is, again, the need to review risk in
6 these specific contexts, to provide us some information
7 on C and D as well.

8 DR. WINTERSTEIN: So the focus is on C and D.

9 Dr. DiGiovanna?

10 DR. DIGIOVANNA: So I'll reiterate what I had
11 suggested first, that, for example, with isotretinoin
12 in teenagers, the disease being treated is usually
13 acne, and for neuroblastoma where you're treating
14 children, it's vastly different and the risk just
15 doesn't exist. That may be an extreme example, but I
16 think that if you're treating, for example, in the
17 post-transplant population, they're usually adults,
18 they're usually quite sick, they're often on many other
19 medications and immunosuppressives, and I think the
20 risk then becomes a different sort of risk. So I fit
21 on that side of the component, and I think that in
22 certain circumstances it makes a difference, and in

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1 others it makes less of a difference.

2 DR. WINTERSTEIN: Dr. Shapiro?

3 DR. SHAPIRO: So, again, I am not qualified
4 to get into the weeds about how to do this, but I do
5 think that the two objectives lend themselves to an
6 answer to your question. So what you want to try to do
7 is maximize the health of the pregnant woman given her
8 underlying condition for which this drug is necessary,
9 and the severity, and your point is well taken, who
10 decides? How is that decided? I can't do it, but it
11 needs to be done. The severity, the alternatives, the
12 effectiveness of the drug, the safety of the drug, all
13 of that would go into that consideration.

14 And you also want to minimize any adverse
15 effects on the fetus, and so to that end, C and D may
16 be important because it's less necessary to worry about
17 that when you're dealing with people who know what
18 they're doing anyway, so you can minimize the barriers
19 because you're dealing and see what people who know
20 what to do anyway. How you know that they know, I
21 don't know, but assuming that you know that they know,
22 but that's again a question I can't weigh in on.

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1 And presence of existing pregnancy
2 prevention, things that are already there, again, I
3 don't know if that ever exists or how commonly it
4 exists or how comprehensive that is, but to the extent
5 that it is, then that would suggest less rather than
6 more of a need for more restriction because you're
7 trying to do those two things.

8 DR. WINTERSTEIN: With respect to C and D, I
9 was thinking through the types of REMS we are talking
10 about and the types of scenarios that I have heard, and
11 so the scenarios where the idea was that the REMS
12 should be simplified, actually those care settings
13 where the REMS are actually extremely easy to
14 implement, I mean, even the more restrictive versions
15 of it.

16 I mean, these were all scenarios where a
17 patient repeatedly sees his physician, this is a highly
18 specialized environment, the physicians are probably
19 used and being certified to all kinds of things
20 already. I'm not absolutely sure whether a
21 simplification would even have an effect because as we
22 are talking about the treatment of somebody who has

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1 cancer and who is going for his radiology or whatever
2 he is doing regularly anyways, and he's in a very
3 highly specialized care environment and being treated
4 by providers who are familiar with the prevention,
5 identifying, monitoring, of teratogenic effects, aren't
6 they implementing the REMS already anyways? I mean,
7 where would be the access or the burden issue in these
8 types of scenarios? I'm trying to come up with a
9 scenario where this actually is a problem, and I'm not
10 finding one.

11 DR. SLATKO: The scenario that hasn't played
12 out but could be a problem is that we assume that the
13 specialists already have the know-how and all they need
14 to do is be primarily educated, that with education
15 they will implement, in essence, the kinds of controls,
16 and rather than requiring them, we just educate and
17 they will implement. And it's not infrequent that that
18 rationale comes up in discussions, not necessarily
19 around teratogenicity only, but in other circumstances
20 where there is an assumption that these physicians know
21 how to do X, and so we don't need to control their
22 behavior, but, rather, all we have to do is provide

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1 training and educational information. And as was
2 stated earlier, I don't know that there is enormous
3 evidence that that assumption is valid, but it is
4 present in these considerations.

5 DR. WINTERSTEIN: That doesn't really seem to
6 be an issue of indication, that seems to be an issue of
7 exceptions of specific provider specialties from a
8 specific educational component of a REMS.

9 DR. SLATKO: Where it can come up is if we're
10 trying to decide whether we need an Element to Assure
11 Safe Use kind of program or a communication plan only
12 kind of program. We may err in the direction of simply
13 proposing or approving a communication plan type of
14 program under the assumption that the physicians have
15 the know-how already. And it might set where the REMS,
16 the initial REMS, is approved at a lower level than
17 might eventually be necessary. That's the scenario.

18 It is theoretical in the teratogenicity area,
19 because as you know, as you saw, we have very few
20 programs that are communication plan only. But if
21 we're heading in the direction in the future of
22 reducing burden and improving access, it might be that

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1 we might be doing more of those kinds of programs in
2 the future.

3 DR. WINTERSTEIN: Yeah, but at the risk of
4 repeating myself, that still seems to be tied towards
5 the provider type and not necessarily the indication.
6 And, I mean, I understand that with the original
7 indication or the original approval of the medication,
8 there might be a deferred or default provider type, and
9 that is probably not a good idea considering the fact
10 that there may be off-label use or other indications
11 and so forth. So if the drug is not restricted to only
12 that provider type having the ability to prescribe the
13 drug, then there is the risk that that communication
14 plan might not be sufficient anyways. But, again, it
15 really is not the indication, I think it depends on
16 whether you can assume that only that particular
17 specialty is prescribing.

18 Dr. Fingert. Dr. Whitaker.

19 DR. GREENE: It seems to me that when
20 Accutane was originally approved and was still on
21 patent, part of the program that Roche instituted was
22 providing reimbursement for a consultation with a

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1 gynecologist to discuss the type of contraception that
2 the patient would use. So it was an implicit
3 acknowledgment of the fact that the one specialist who
4 was going to prescribe the drug was not intimately
5 familiar with the risks and benefits of various methods
6 of contraception and that they were going to direct the
7 patient, at the company's expense, to a specialist who
8 was familiar with those issues.

9 I think that many of the drugs, whether it's
10 mycophenolate, which is going to be prescribed by the
11 transplant surgeon, or isotretinoin, that's going to be
12 prescribed by the dermatologist, or ribavirin, that's
13 going to be prescribed by the hepatologist, that meets
14 that same criteria, that the person prescribing the
15 medication that is potentially problematic isn't also
16 familiar with and comfortable with the expertise
17 necessary to counsel the patient about appropriate
18 methods for contraception and most efficacious methods.

19 So I do think there are issues with respect
20 to which specialists are prescribing which drugs. For
21 the most part, it's not going to be the gynecologist
22 that's going to be prescribing these medications.

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1 DR. WINTERSTEIN: Dr. Fingert?

2 DR. FINGERT: Well, building on Dr. Greene's
3 comments, I'm wondering if the panel members or the
4 Agency see any mechanisms whereby industry can partner
5 and get more training or education back to the
6 prescriber community so that it would better enable
7 more reliability and compliance with these issues.

8 I think in oncology there has been some
9 strong collaboration when new drugs have been
10 introduced and working with the oncology community
11 about understanding their risks. And here, too, do you
12 think that there is hope that that sort of thing should
13 be done through organizations like PERI? There is an
14 organization called the Pharmaceutical Education Research
15 Institute that has as its mission to help provide
16 education more commonly among the pharmaceutical
17 companies and also among other stakeholders that share
18 the proper use of these drugs.

19 DR. WINTERSTEIN: Dr. Whitaker?

20 DR. WHITAKER: I was just going to say I
21 agree with what you were saying, that these are
22 fundamentally different issues, and as someone who had

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1 such a strong opinion about A, the medical condition, I
2 think that C and D are very different issues, that they
3 don't necessarily correlate, that just because we may
4 do things differently because of the condition, or that
5 I have that belief that we should do things a little
6 differently when the condition is severe, that the
7 treatment environment -- I guess I just want to say I
8 agree with Dr. Greene, and Dr. Chambers said it
9 earlier, that just because somebody is getting their
10 treatment in a very specialized environment by
11 oncologists who know a lot about oncology, as someone
12 who specializes in contraception and contraceptive
13 counseling, the myths and false information out there
14 abound.

15 Just like I don't know a lot about drugs that
16 treat cancer, I find that specialists in other fields
17 often have very -- well, I don't want to say mainly,
18 but often do perpetuate some of the myths about
19 contraception and that it would be great to assume that
20 they're going to get good contraceptive counseling, but
21 that's not been my experience.

22 DR. WINTERSTEIN: Dr. Kaboli?

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1 DR. KABOLI: So it's getting late and my
2 brain is starting to slow down, so I'm not sure where
3 this last part of the discussion was really going, but
4 it seems like this last question, though, fits in with
5 the issue of the focused REMS or a directed REMS but
6 also the theoretical framework that should be
7 developed.

8 There is a whole section on the extrinsic
9 factor and clinical use-related factors including the
10 medical condition, patient population, context of care.
11 I think that's what a lot of this is falling under. And
12 right now we're sort of talking theoreticals, because
13 I'm looking through the list and I'm thinking, what
14 would be a specific example? And I really can't think
15 of any.

16 The only theoretical one that I could even
17 come up with is something like bosentan, which is used
18 for a very severe condition, of pulmonary arterial
19 hypertension, but what if you found out that you could
20 take one tablet a year for prophylaxis? And it's a
21 very rare condition, but now you're going to have
22 primary care providers doing prophylaxis at a very

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1 dose, so the risk is small, but the potential -- you
2 know, each drug becomes its own specific condition and
3 context.

4 So I really feel like -- I'm sure I'm going
5 all over the place here at this last -- at the end
6 here, so Chairperson --

7 (Laughter.)

8 DR. WINTERSTEIN: Thank you, Dr. Kaboli. Very
9 helpful.

10 (Laughter.)

11 DR. WINTERSTEIN: Where we were here?

12 Dr. Yao.

13 DR. YAO: It was actually to Dr. Fingert's
14 point, but thank you for the other folks who weighed in
15 on Item C, and I guess sort of to the same extent Item
16 D, and I think what I heard is that there is really no
17 guarantee that you know who is going to be doing the
18 counseling for any particular situation, even if you
19 think that the use will be very limited. And so that's
20 very helpful for us to understand.

21 And then as it relates to strategies for
22 improving education, that will be a major focus of

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1 tomorrow, so we would like to hear your comments there.

2 DR. WINTERSTEIN: Dr. Chambers.

3 DR. CHAMBERS: So I just wanted to make
4 another pitch for C, that I think that the various
5 prescriber types, that it can't be assumed that one is
6 any better than the other except perhaps for the
7 contraceptive counseling specialist, if there happened
8 to be a drug that that prescriber was responsible for
9 giving to women of reproductive age, and that the idea
10 that Mike brought up of having access to contraceptive
11 counseling that was part of the original Accutane
12 program, I would be curious to know how many people
13 actually took advantage of that. It may have been very
14 few. But the idea not only that the contraceptive
15 counseling would be made available by a specialist but
16 also that the person would be encouraged to take
17 advantage of that and that the person who provided it
18 knew they were doing it for the reason that this is
19 prevention of pregnancy that might involve a
20 teratogenic exposure as opposed to just -- and I think
21 it's just a highly unique situation and it certainly,
22 as my colleague here knows better than I do, that when

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1 it comes to talking to somebody who is from a different
2 culture or Spanish-speaking or whatever, that there are
3 very specific issues related to contraception, that
4 it's literally impossible to ask the neurologist or the
5 rheumatologist to be able to be competent in doing that
6 across the board.

7 DR. WINTERSTEIN: Those were much better
8 final words than Dr. Kaboli's final words I would like
9 to say.

10 (Laughter.)

11 DR. WINTERSTEIN: But you have tomorrow to
12 improve.

13 (Laughter.)

14 DR. WINTERSTEIN: If you would like to keep
15 your handouts, you need to take them with you because
16 tomorrow they won't be here anymore, I was advised to
17 tell you. And if you would like to leave your name tag
18 here, this way you won't forget it in the hotel
19 tomorrow, that might be a handy thing to do as well.

20 Is the FDA happy with what we did? I mean,
21 I'm happy, but I'm not sure whether --

22 DR. SLATKO: Yes. Thank you. (Off

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1 microphone.)

2 DR. WINTERSTEIN: Yes? Well, then I would
3 like to thank everyone. I thought this was actually a
4 very, very constructive discussion. I was much more
5 afraid that we would not come up with anything and get
6 lost, but I think we did not. And I look forward to
7 continuing tomorrow. Have a good evening.

8 And I have to read something I am sure.

9 Okay, we will now adjourn the evening. Panel
10 members, please remember that there should be no
11 discussion of the meeting topics amongst yourselves or
12 with any member of the audience while we are adjourned.
13 We will resume tomorrow morning at 8:00 a.m.

14 (Whereupon, at 5:10 p.m., Day 1 of the
15 Meeting of the Drug Safety and Risk
16 Management Advisory Committee (DSaRM) was adjourned.)

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2 I, RICK SANBORN, the officer before whom the
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Notary Public in and for
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