

**Summary Minutes of the Drug Safety and Risk Management Advisory Committee Meeting  
December 12, 2012**

**Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference  
Center  
(Rm. 1503), Silver Spring, MD**

**All external requests for the meeting transcripts should be submitted to the CDER, Freedom  
of Information office.**

**These summary minutes for the December 12, 2012 Meeting of the Drug Safety and Risk  
Management Advisory Committee of the Food and Drug Administration were approved on  
2/26/13 \_\_\_\_.**

**I certify that I attended the December 12, 2012 meeting of the Drug Safety and Risk  
Management Advisory Committee and that these minutes accurately reflect what transpired.**

\_\_\_\_\_/s/\_\_\_\_\_  
**Nicole Vesely, PharmD  
Acting Designated Federal Officer  
Drug Safety and Risk Management Advisory  
Committee**

\_\_\_\_\_/s/\_\_\_\_\_  
**Almut Winterstein, PhD  
Acting Chairperson**

**for**

**Kristina Toliver, PharmD  
Designated Federal Officer  
Drug Safety and Risk Management Advisory  
Committee**

The Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 12, 2012 at the FDA White Oak Campus, Great Room (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA. The meeting was called to order by Almut Winterstein, PhD (Acting Chairperson); the conflict of interest statement was read into the record by Kristina A. Toliver, PharmD (Designated Federal Officer). There were approximately 50 persons in attendance. There were three Open Public Hearing speakers.

**Issue:** The Food and Drug Administration Amendments Act of 2007 requires FDA to bring, at least annually, one or more drugs with Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) before CDER's Drug Safety and Risk Management Advisory Committee (DSaRM). On December 12, 2012, the Agency presented information on the risk management of teratogens, some of which have REMS with ETASU. The DSaRM advisory committee met to discuss the various strategies used by the Agency to define and address teratogenic risk, including requiring REMS with ETASU. The discussion included an evaluation of the different strategies and the decision framework for selecting risk management strategies for teratogens. The committee discussed whether the risk management strategies, including REMS with ETASU, assure safe use, are not unduly burdensome to patient access to the drug, and to the extent practicable, minimize the burden to the health care delivery system.

**Attendance:**

**Drug Safety and Risk Management Advisory Committee Members Present (Voting):**

Brian Erstad, PharmD; Sonia Hernandez-Diaz, MD, DrPH; Peter Kaboli, MD; David Madigan, PhD; Elaine Morrato, DrPH; Maria Suarez-Almazor, MD, PhD; Almut Winterstein (Acting Chairperson), PhD; T. Mark Woods, PharmD

**Temporary Members (Voting):**

Susan Broyles (Patient Representative); Christina Chambers, PhD, MPH; Elizabeth Conover, MSN; Janet Cragan, MD; John J. DiGiovanna, M.D.; Elaine Francis, PhD; Michael Green, MD; Kathleen Hoeger, MD, MPH; James Liebmann, MD; Michael Menefee, MD; Janine Polifka, MD; Sonja Rasmussen, MD, MS; Robyn Shapiro, JD; Angelica Walden (Patient Representative), Amy Whitaker, MD, MS; Katherine Wisner, MD, MS (Speaker and Discussant); Michael Wolf, PhD, MPH (via phone)

**Acting Industry Representative to the Drug Safety and Risk Management Advisory Committee (Non-Voting):**

Howard Fingert, MD, FACP (Acting Industry Representative)

**Drug Safety and Risk Management Advisory Committee Members Not Attending:**

Patrizia Cavazzoni, MD (Industry Representative); William Cooper, MD; Sherine Gabriel, MD (Chairperson); Karen Hopkins, MD (Consumer Representative); Jeanmarie Perrone, MD, FACMT; Marjorie Shaw Phillips, MS, RPh, FASHP;

**FDA Participants (Non-Voting):** Mwango Kashoki, MD, MPH; Claudia Manzo, PharmD; Gary Slatko, MD, MBA; Melissa Tassinari, PhD; Lynne Yao, MD

**Guest Speakers (Non-Voting, Presenting Only):** Beth Choby, MD; Kate Ryan MPA

**Designated Federal Officer:** Kristina A. Toliver, Pharm.D.

**Open Public Hearing Speakers:**

Mercedes Benegbi – Executive Director, Thalidomide Victims Association of Canada

Joe Nadglowski – President, Obesity Action Coalition (OAC)

Brandel France de Bravo, MPH – Director of Public Affairs and Communications, National Research Center for Women & Families/Cancer Prevention and Treatment Fund

***The agenda was as follows:***

|  |   |
|--|---|
| Call to Order and Opening Remarks<br>Introduction of Committee                         | <b>Almut Winterstein, PhD</b><br>Acting Chairperson, Drug Safety and Risk Management Advisory Committee (DSaRM)   |
| Conflict of Interest Statement   | <b>Kristina A. Toliver, PharmD</b><br>Designated Federal Officer, DSaRM   |
| Opening Remarks  | <b>Claudia Manzo, PharmD</b><br>Director, Division of Risk Management (DRISK)<br>Office of Surveillance and Epidemiology (OSE),<br>Center for Drug Evaluation and Research (CDER),<br>FDA |
| <b><u>FDA Presentations</u></b>  |   |
| Evidence for Teratogenic Risk:<br>Assessment of Animal and Human<br>Data               | <b>Melissa S. Tassinari, PhD DABT</b><br>Acting Team Leader – Maternal Health Team<br>Pediatric and Maternal Health Staff (PMHS)<br>Office of New Drugs (OND), CDER, FDA                  |
| Retrospective review of FDA’s<br>teratogenicity risk management<br>approaches          | <b>Mwango Kashoki, MD, MPH</b><br>Associate Director for Safety<br>Team Leader - Safety Policy and Research Team<br>OND, CDER, FDA  |
| Teratogenic drugs:<br>Evaluation of the effectiveness<br>of risk management strategies | <b>Doris Auth, PharmD</b><br>Team Leader– REMS Assessment Team<br>DRISK/OSE, CDER, FDA  |
| Framework for Decisions to Manage<br>Teratogenic Risk                                  | <b>Amarilys Vega, MD, MPH</b><br>Risk Management Analyst<br>DRISK/OSE, CDER, FDA  |
| Example of a Teratogenic Risk<br>Management Decision                                   | <b>Mary Ross Southworth, PharmD</b><br>Deputy Director for Safety<br>Division of Cardiovascular and Renal Products<br>OND, CDER, FDA  |
| Clarifying Questions for the Presenters  |   |

**BREAK**

**Industry Perspective:** Management of the teratogenic potential of drug products

**John Freeman, MSc, BSc (Hons), LLB Hons)**  
Corporate Vice President  
Global Drug Safety & Risk Management,  
Celgene Corporation

Clarifying Questions for the Presenter

**Special Presentations:**

*Prescriber perspective:* Clinical management of non-pregnant females of reproductive potential, who require treatment with teratogenic drug(s)

**Beth Choby, MD (Guest Speaker)**  
Associate Professor  
Department of Family Medicine  
University of Tennessee Health Sciences Center

*Prescriber perspective:* Clinical management of pregnant females requiring treatment with teratogenic drug(s)

**Katherine Wisner, MD, MS (Speaker and Discussant)**  
Asher Professor of Psychiatry and Obstetrics and Gynecology  
Director, Asher Center for Research and Treatment of Depressive Disorders  
Northwestern University  
Feinberg School of Medicine

*Patient perspective:* Female patients of reproductive potential experience with teratogenic drug(s)

**Kate Ryan, MPA (Guest Speaker)**  
Senior Program Coordinator  
National Women's Health Network

Clarifying Questions for the Speakers

**LUNCH**

Open Public Hearing

Questions to the Committee/  
Committee Discussion

**BREAK**

Questions to the Committee/  
Committee Discussion (cont)

**ADJOURNMENT**

### ***Questions to the Committee:***

#### Drug Safety and Risk Management Advisory Committee Questions: December 12, 2012

The Agency is seeking input from the Committee on issues related to management of teratogenic risk in female patients of reproductive potential, and female partners of male patients treated with teratogenic drugs. The following non-voting questions will be discussed by the committee members:

1. **(DISCUSSION)** Discuss FDA's decision framework for selecting strategies to manage a drug's teratogenic risk, specifically:
  - a. Discuss whether the framework appropriately reflects all of the factors that should be considered when determining how a drug's teratogenic risk should be managed.
  - b. Provide your recommendations as to which factors in the framework are key for determining when labeling is sufficient to manage the teratogenic risk.
  - c. Provide your recommendations as to which factors in the framework are key for determining when a risk evaluation and mitigation strategy (REMS) is also necessary to manage the teratogenic risk.

***Committee Discussion:*** Questions 1-a through 1-c were discussed together. The committee stated that there is a need for more data. More quantitative data is needed on effectiveness of REMS and the burden of REMS. The committee questioned how much more of an incremental gain does a more restrictive REMS give compared to a less-restrictive REMS. The committee noted that the burden of risk management seems to increase as the burden of managing teratogenicity of the treatment increases. Specifically, the committee proposed that risk could be quantified as the numbers needed to harm times the overall exposure prevalence and the expected severity of birth defects. There were also questions about how to impute animal data to clinical data. The committee was also concerned about the lack of phase 4 studies that address concerns about teratogenicity. With regard to the framework, the committee stated that it was a good start, however they noted that the application of the framework needs more explicit guidelines about how and when the factors listed in the framework can be used to determine whether or not a REMS is necessary for a teratogenic drug, including a restrictive REMS. The committee acknowledged that the data needed to do this may not be currently available. Please see transcript for detailed discussion.

2. **(DISCUSSION)** Discuss the adequacy of the current definition of females of reproductive potential (FRP), and whether the definition includes the necessary identifying characteristics.

The definition of females of reproductive potential is: girls who have entered puberty and all women who have a uterus and have not passed through menopause.

***Committee Discussion:*** The committee stated that, overall, the definition is appropriate. The committee noted that because the definitions of puberty and menopause themselves have some subjectivity and limitations, this can impact the adequacy of the FRP definition. The committee stated that the "at risk" population needs to be more objectively defined. Please see transcript for detailed discussion.

3. **(DISCUSSION)** Under certain circumstances, females – either pregnant or of reproductive potential - who are *partners* of male patients taking a teratogenic drug can be considered "at-risk" populations. Discuss what evidence or considerations are important for determining when these groups are "at-risk."

**Committee Discussion:** *The committee stated that there is limited information on when and how a teratogenic risk might be imposed to females through their male partners who are taking teratogenic drugs. Several members of the committee stated that concerns for most drugs are based on a theoretical risk and the limited evidence suggested a low plausibility of potential risk even if the drug were present in the semen. Until the nature or extent of that risk is known, it's very hard to make a decision regarding what evidence or considerations are important. The committee stated that based on the limited plausibility of such a risk, it may not be necessary to consider this group of females as "at-risk" for teratogenicity.*

4. **(DISCUSSION)** In the Committee's view,
  - a. What would be the benefits of implementing a targeted REMS program for a teratogenic drug to specific "at-risk" populations?
  - b. What are the potential negative consequences of implementing a targeted REMS program for a teratogenic drug to specific "at-risk" populations?

Include in the discussion the feasibility of designing and successfully implementing a targeted risk management program and the potential impact of a targeted program on patients' access to drug and potential burden(s) to the healthcare system.

**Committee Discussion:** *Questions 4-a and 4-b were discussed together. The committee overall found that when possible, a REMS should be targeted to the "at risk" population. However, the committee noted that decisions about when to target a REMS are highly context-dependent, and are influenced by such factors as the type of drug, the type and experience of the providers who will prescribe or treat patients taking the drug. The committee noted that to restrict beyond definitions such as gender [i.e., restrict only to females or males] require 'diagnostic validity' of the 'at-risk' group. The committee proposed that, if there is a greater potential for inappropriate sharing of the teratogenic medication (e.g., with an oral medication that is used for a common condition), a targeted REMS program may not be indicated. Please see transcript for detailed discussion.*

5. **(DISCUSSION)** Occasionally, the same teratogenic drug may be used for different treatment indications (medical conditions). Provide your recommendations as to whether or not a consistent risk management approach should be employed for a teratogenic drug irrespective of whether it is used to treat different medical conditions. Discuss the following factors that might influence your decision and their relative importance for such a decision:
  - a. The medical condition being treated (e.g., obesity, diabetes mellitus, seizures)
  - b. The characteristics of the patient population likely to use the drug (e.g., proportion or total number of females of reproductive potential; those likely to use the drug for off-label indications)
  - c. The familiarity of the various prescriber types with preventing, identifying, and/or monitoring for teratogenic effects
  - d. The presence of existing pregnancy prevention and/or monitoring safeguards within the expected treatment setting (e.g., routine pre-admission pregnancy testing of female patients)

**Committee Discussion:** *Questions 5-a through 5-d were discussed together. The committee generally concluded that because a drug's teratogenic risk is the same, regardless of the medical condition, the risk management strategies should be tailored around the risk itself, and not around the medical condition. However, the committee favored implementation of a REMS for a teratogen used in multiple indications in such a way that the program facilitates access for patients with severe conditions. The committee noted there may be difficulty in defining what is a "severe" condition (for example, is cancer a more severe*

*condition than major depression, or vice versa?). Some committee members noted that a focus on specific indications may not be feasible. There was a recommendation for a tiered approach to a REMS for a teratogen used in multiple indications: more restrictive REMS should be used when treating symptomatic conditions, and less restrictive REMS when treating more severe conditions. Off-label use was noted as a concern when determining the type of REMS by indication. With regard to familiarity of healthcare providers with preventing, identifying, and/or monitoring for teratogenic effects, it was stated it can't be assumed that one type of provider or treatment setting is better at doing these things than another. Additionally, in the clinic setting, it may not be the actual prescriber or physician who will be counseling female patients about the risks of a teratogenic drug or contraceptive use. The committee recommended that strategies should be implemented for improving healthcare provider education on how to counsel patients on these matters. Please see transcript for detailed discussion.*

The meeting was adjourned at approximately 5:30pm.