Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products: An Institute of Medicine Workshop

May 12, 2014

U.S. Food and Drug Administration (FDA) Campus White Oak, Maryland

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Background and Meeting Objectives:

There is increasing attention on the need for enhancing the evaluation and communication of the benefits and risks associated with pharmaceutical products, thereby increasing the predictability, transparency, and efficiency of pharmaceutical regulatory decision-making. In 2006, the IOM's Forum on Drug Discovery, Development, and Translation held a workshop to explore the complex tradeoff between drug benefits and risks and examine approaches for better quantifying this balance and informing the public and the medical community. Since that time, FDA has worked to develop an enhanced structured approach to the assessment of benefits and risks in drug regulatory decision-making to better communicate this aspect of the human drug review process. FDA envisions that this framework will serve as a template for product reviews, as well as a vehicle for explaining the basis for FDA's regulatory decisions.[1] FDA's work in this area coincides with efforts by other regulatory agencies, academia, and the pharmaceutical industry.

As FDA's draft PDUFA V Implementation Plan (the Plan) indicates, an extensive body of evidence informs regulatory decisions on the safety and efficacy of a proposed product, but in many cases, FDA must draw conclusions from imperfect data. Identifying and evaluating sources of uncertainty (e.g., absence of information, conflicting findings, marginal results) in a regulatory application is an important part of reviewers' work; however, drawing conclusions in the face of uncertainty can be a complex and challenging task. Effectively communicating regulatory decisions necessarily includes explanation of the impact of uncertainty on decision-making. Uncertainty may arise from many sources; however two particular areas of uncertainty that could benefit from additional attention are (1) the translation of pre-market clinical trial data to the post-market setting in which an approved drug is used in a much wider patient population, and (2) new findings that emerge in a post-marketing setting where the basis for the finding comes from sources of varying levels of rigor.

This two-part public workshop series will address the opportunity to advance the development of more systematic and structured approaches to characterize and communicate (a) the sources of uncertainty in the assessment of benefits and risks; and (b) their implications for pharmaceutical regulatory decisions. Specifically, the workshop series will explore potential analytical and communication approaches and identify key considerations on their development, evaluation, and incorporation into the assessment of benefits and risks in pharmaceuticals. This workshop

[1] FDA's structured approach to benefit-risk assessment in drug regulatory decision-making is outlined in the Draft PDUFA V Implementation Plan [February 2013], available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

series will consider the entire drug development lifecycle, including pre-market drug review and post-market safety surveillance.

The workshop series objectives are to:

- Discuss the challenges in applying more systematic approaches to characterizing and communicating uncertainty in the assessment of a drug's benefits and risks.
- Identify potential systematic approaches to address uncertainty faced by regulators in the assessment of benefits and risks in pharmaceuticals, drawing from various scientific and regulatory disciplines and domains.
- Identify possible principles, best practices, and resources that can facilitate the development, evaluation, and incorporation of such approaches in regulatory decision-making.
- Explore principles and approaches to facilitate the communication about uncertainty in the assessment of benefits and risks with FDA stakeholders.

Second Workshop in the Series

9:00 a.m. Welcome and Opening Remarks

BARUCH FISCHHOFF, *Workshop Co-Chair*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

ROBERT RATNER, *Workshop Co-Chair*
Chief Scientific and Medical Officer
American Diabetes Association

SESSION I: REFLECTIONS ON CHARACTERIZING UNCERTAINTY: LESSONS FROM THE FIRST WORKSHOP

Session Objectives:

- Discuss objectives of the first workshop.
- Identify key themes from the first workshop.
- Discuss how lessons and observations from the first workshop could support the advancement of approaches to characterizing uncertainty in the assessment of benefits and risks and their implications for pharmaceutical regulatory decisions.

BARUCH FISCHHOFF, *Workshop Co-Chair, Session Chair*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

9:05 a.m. **The Challenge of Uncertainty in Regulatory Decision-Making** (*20 min.*)

PATRICK FREY
Director, Office of Program and Strategic Analysis
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

9:25 a.m. **Key Messages and Potential Lessons Learned** (*30 min.*)

BARUCH FISCHHOFF, *Workshop Co-Chair*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

PAUL SELIGMAN
Executive Director, U.S. Regulatory Policy
Amgen Inc.

Discussion Question:

- How can the concepts discussed in day 1 be applied and operationalized in characterizing uncertainty in pharmaceutical product evaluation?

9:55 a.m. **BREAK** (*15 min.*)

SESSION II: OVERVIEW OF REGULATORY STRATEGIES ABOUT UNCERTAINTY IN THE BENEFIT AND RISK ASSESSMENT

Session Objectives:

- Provide an overview of regulatory strategies for communicating benefits and risks of pharmaceutical products and clarify the drug regulator's role in communicating uncertainty.
- Discuss FDA's Patient-Focused Drug Development Initiative and consider the ways in which FDA receives information from different stakeholders and incorporates this information into addressing the relevant uncertainties in the assessment of benefits and risks.

10:10 a.m. Background and Session Objectives (*5 min.*)

ROBERT RATNER, *Workshop Co-Chair*
Chief Scientific and Medical Officer
American Diabetes Association

10:15 a.m. **Challenges to the Regulator in Communicating Uncertainties in Risks of Approved Pharmaceuticals** (*15 min*.)

MARY PARKS
Deputy Director, Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

10:30 a.m. **FDA Patient-Focused Drug Development Initiative** (*15 min*.)

THERESA MULLIN
Director, Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

10:45 a.m. **Health Canada's Approach to Uncertainty Within its Benefit–Harm–Uncertainty Initiative** (*15 min.*)

ROBYN LIM
Senior Science Advisor, Office of Legislative and Regulatory Modernization
Health Products and Food Branch
Health Canada

11:00 a.m. Discussion with Speakers and Audience (*20 min.*)

Discussion Moderator: Robert Ratner, Chief Scientific and Medical Officer, American Diabetes Association

Discussion Topics:

- How can the patient voice inform how much uncertainty can be tolerated?
- How do we communicate information about what is known and unknown about benefits and risks as that information changes?

SESSION III: COMMUNICATING UNCERTAINTY ABOUT BENEFIT AND RISK ASSESSMENTS

Session Objectives:

- Understand and consider the implications of the communication of uncertainty about benefit and risk assessments on the health care system beyond drug regulatory decision-making.
- Understand a patient perspective on what is important to patients in understanding the assessments of benefit and risk and how patients want to receive and share information about uncertainty.
- Consider methodological challenges in communication strategies and suggest approaches for overcoming the "false precision" that can arise in assigning probabilities to patient outcomes.
- Suggest principles and approaches to improve the communication about uncertainty in the assessment of benefits and risks to FDA stakeholders.

11:20 a.m. Background and Session Objectives (*5 min*.)

ROBERT RATNER, *Workshop Co-Chair*
Chief Scientific and Medical Officer
American Diabetes Association

11:25 a.m. **Overview of Risk Communication** (*15 min*.)

BARUCH FISCHHOFF, *Workshop Co-Chair*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

11:40 a.m. **Risk Communication in the Context of Pharmaceuticals** (*15 min*.)

LISA SCHWARTZ
Professor, Departments of Medicine and Community & Family Medicine
Dartmouth Medical School
Co-Director, Medicine in the Media Program
The Dartmouth Institute for Health Policy and Clinical Practice

STEVEN WOLOSHIN
Professor, Departments of Medicine and Community & Family Medicine
Dartmouth Medical School
Co-Director, Medicine in the Media Program
The Dartmouth Institute for Health Policy and Clinical Practice

11:55 a.m. **What Are the Sources of Uncertainty When a Patient Is Faced With Choice?** (*15 min.*)

K. KIMBERLY MCCLEARY
Director of Strategic Initiatives
FasterCures

12:10 p.m. **LUNCH** (*40 min.*)

12:50 p.m. **Re-introducing the Tysabri Case Study** (*15 min.*)

ROBERT TEMPLE
Deputy Director for Clinical Science
Acting Deputy Director, Office of Drug Evaluation I
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

1:05 p.m. **Media Analysis: Tysabri Case Study** (*20 min.*)

LISA SCHWARTZ
Professor, Departments of Medicine and Community & Family Medicine
Dartmouth Medical School
Co-Director, Medicine in the Media Program
The Dartmouth Institute for Health Policy and Clinical Practice

STEVEN WOLOSHIN
Professor, Departments of Medicine and Community & Family Medicine
Dartmouth Medical School
Co-Director, Medicine in the Media Program
The Dartmouth Institute for Health Policy and Clinical Practice

1:25 p.m. **Discussion on Communicating Uncertainty in Benefit and Risk Assessments of Pharmaceutical Products: Tysabri and Beyond** (*60 min.*)

Session III Speakers and:

CARMEN BOZIC
Senior Vice President
Clinical and Safety Sciences
Biogen Idec

ROBERT FOX
Staff Neurologist
Mellen Center for MS
Cleveland Clinic

ALICE HUGHES
Supervisory Medical Officer
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

JOYCE KORVICK
Deputy Director for Safety, Division of Gastroenterology and Inborn Error Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

CYNTHIA SITCOV
Patient Representative and Voting Member
U.S. Food and Drug Administration, Central and Peripheral Systems Advisory Committee, 2005–Present

Discussion Moderator: Gavin Huntley-Fenner, Human Factors and Safety Consultant, Huntley-Fenner Advisors

2:25 p.m. **BREAK** (*15 min.*)

2:40 p.m. **Public Comment Period** (*30 min.*)

SESSION IV: CONCLUDING DISCUSSION: LESSONS LEARNED AND POTENTIAL STRATEGIES FOR A WAY FORWARD

Session Objectives:

- Discuss key themes from the workshop series.
  - What are key techniques and approaches for identifying, characterizing, and addressing uncertainty?
  - How do we communicate uncertainty in evidence regarding benefit-risk assessment?
- Describe key gaps in understanding and explore how best to address those gaps.
- Highlight potential pivotal opportunities to advance more systematic and structured approaches to characterizing and communicating the sources of uncertainty in the assessment of benefits and risks.
  - How do we shape an agenda for next steps to address these issues?

3:10 p.m. Reflections from the Workshop Co-Chairs (*10 min.*)

BARUCH FISCHHOFF, *Workshop Co-Chair*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

ROBERT RATNER, *Workshop Co-Chair*
Chief Scientific and Medical Officer
American Diabetes Association

3:20 p.m. **Brainstorming Discussion of Key Themes From the Workshop Series** (*90 min.*)

3:20 p.m. **Segment One: Identifying and Mitigating Uncertainty Through Maximizing the Value of Evidence**

Reflections from Discussion Lead

Discussion Lead: Robert Temple, U.S. Food and Drug Administration (*5 min.*)

3:25 p.m. Discussion with Workshop Participants (*15 min.*)

3:40 p.m. **Segment Two: Characterizing and Understanding Uncertainties**

Reflections from Discussion Lead

Discussion Lead: Paul Seligman, Amgen Inc. (*5 min.*)

3:45 p.m. Discussion with Workshop Participants (*15 min.*)

4:00 p.m. **Segment Three: Eliciting Values From Stakeholders, Particularly Patients**

Reflections from Discussion Lead

Discussion Lead: K. Kimberly McCleary, FasterCures (*5 min.*)

4:05 p.m. Discussion with Workshop Participants (*15 min.*)

4:20 p.m. **Segment Four: Communicating Uncertainty About Benefit and Risk Assessments of Pharmaceutical Products**

Reflections from Discussion Lead

Discussion Lead: Gavin Huntley-Fenner, Huntley-Fenner Advisors (*5 min.*)

4:25 p.m. Discussion with Workshop Participants (*15 min.*)

4:40 p.m. **Reflecting on Tactics and Strategies for A Way Forward** (*20 min.*)

Discussion Moderators: Workshop Co-Chairs, Baruch Fischhoff, Carnegie Mellon University; and Robert Ratner, American Diabetes Association

5:00 p.m. Adjourn