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

February 12–13, 2014

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

---

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 public workshop 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 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

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

The workshop 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.

Day One

9:00 a.m. 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

9:15 a.m. The Importance of Considering Uncertainty in Regulatory Decision-Making (1*5 min*.)

JANET WOODCOCK
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

SESSION I: APPROACHES TO EVALUATE UNCERTAINTY: MAXIMIZING THE VALUE OF THE EVIDENCE

Session Objectives:

- Discuss potential methods (proven and yet to be tried) to identify and evaluate sources of uncertainty. What structured systematic approaches to evaluating uncertainties could be considered by regulators?
- Acknowledge and discuss challenges in both identifying and addressing uncertainty in drug regulation.

9:30 a.m. Background and Session Objectives (*5 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

9:35 a.m. **Key Sources of Uncertainty in the Assessment of Benefits and Risks of Pharmaceuticals and Associated Challenges** (*15 min.*)

TAREK HAMMAD
Executive Director, Epidemiology
Merck Research Laboratories
Merck & Co., Inc.

9:50 a.m. Identifying and Evaluating Uncertainty

Addressing Challenges Arising from the Completeness of Data Collection in Clinical Trials (*15 min.*)

DEBORAH ZARIN
Director, ClinicalTrials.gov
National Library of Medicine
National Institutes of Health

Identifying and Retaining Subgroups in Clinical Trials in the Context of Uncertainty about the External Validity of Clinical Trials (*15 min.*)

MICHAELA KIERNAN
Senior Research Scientist
Stanford Prevention Research Center
Stanford School of Medicine

Research Methodologies to Reduce or Address Uncertainties in the Evaluation of Pharmaceutical Benefits and Risks (*15 min.*)

SEBASTIAN SCHNEEWEISS
Professor of Medicine and Epidemiology
Harvard Medical School

10:35 a.m. Discussion with Speakers and Audience (*20 min.*)

Discussion Moderator: Brian Strom, Chancellor, Biomedical and Health Sciences, Rutgers University

10:55 a.m. BREAK (*15 min.*)

SESSION II: CASE STUDIES: UNCERTAINTY IN THE ASSESSMENT OF BENEFITS AND RISKS OF PHARMACEUTICAL PRODUCTS

Session Objectives:

- Provide an overview of FDA's approach to evaluating benefits and risks of pharmaceutical products and how these approaches take into consideration sources of uncertainty.
- Identify a range of uncertainties faced by drug regulators through presentation of two drug product case studies from FDA, including pre- and post-market experiences. The case studies will illustrate how the uncertainty was considered and addressed in the decision-making process within the constraints of protecting proprietary information.

11:10 a.m. Background and Session Objectives (*5 min.*)

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

11:15 a.m. **FDA Approach to Evaluating Benefits and Risks of Pharmaceuticals** (*10 min.*)

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

11:25 a.m. **Presentation of FDA Case Studies**

Tysabri (natalizumab)/multiple sclerosis (MS) (*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

Anoro Ellipta (umeclidinium and vilanterol inhalation powder)/chronic obstructive pulmonary disease (COPD) (*15 min*)

JENNIFER PIPPINS
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

11:55 a.m. Discussion with Speakers and Audience (*15 min*.)

Discussion Moderator: Patrick Frey, Director, Office of Program and Strategic Analysis, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

12:10 p.m. LUNCH (*50 min.*)

SESSION III: METHODS TO ADDRESS UNCERTAINTY: MAKING SENSE OF FINDINGS FROM THE EVIDENCE

Session Objectives:

- Consider methods, statistical or otherwise, that could be deployed by the regulator to evaluate and address issues of uncertainty in clinical research data.
- Present methods, approaches, and lessons learned from other regulatory domains, which could address the challenges of identification and evaluation of uncertainty in regulatory decision-making.

1:00 p.m. Background and Session Objective (*5 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

1:05 p.m. **Methods to Characterize and Elicit Uncertainty** (*15 min.*)

M. GRANGER MORGAN [*via remote presentation*]
Professor and Head
Department of Engineering and Public Policy
Carnegie Mellon University

1:20 p.m. Addressing Challenges of Identification and Evaluation of Uncertainty

Experiences in Implementing Uncertainty Assessments in the Defense/Intelligence Communities (*15 min.*)

DAVID MANDEL
Senior Scientist
Defence Research and Development Canada, Toronto Research Centre

Systematic Approaches to Assessing the Internal and External Validity of Randomized Controlled Trials (*15 min.*)

JOHN IOANNIDIS [*via remote presentation*]
C. F. Rehnborg Professor in Disease Prevention
Professor of Health Research and Policy
Stanford School of Medicine

Bayesian Approaches to Evaluating Clinical Trial Data (*15 min.*)

JOEL GREENHOUSE
Professor of Statistics
Carnegie Mellon University

2:05 p.m. Discussion with Speakers and Audience (*20 min*.)

Discussion Moderator: Lisa LaVange, Director, Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

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

SESSION IV: REGULATORY DECISION-MAKING UNDER UNCERTAINTY

Session Objective:

- Discuss potential approaches from decision theory that could be used in the regulatory setting (e.g., case studies), acknowledging that approaches will vary in the context of the unique uncertainties presented and that ultimately, the regulator will need to decide.

2:40 p.m. Background and Session Objective (*5 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

2:45 p.m. **Public Policy in an Uncertain World: Analysis and Decisions in Pharmaceutical Benefits and Risks** (*15 min*)

CHARLES MANSKI
Board of Trustees Professor in Economics
Northwestern University

3:00 p.m. Approaches Suggested from Decision Theory to Support Regulatory Decision-Making Under Uncertainty

Approaches to Eliciting Values for Uncertain Choices (*15 min.*)

TIMOTHY MCDANIELS
Faculty of Science
Institute of Resources and Environment
University of British Columbia

Consultative Processes for Acceptable Decisions (*15 min.*)

JOSEPH ARVAI
Svare Chair in Applied Decision Research
Department of Geography
Institute for Sustainable Energy, Environment, and Economy
University of Calgary

3:30 p.m. Discussion with Speakers and Audience (*20 min*.)

Discussion Moderator: Paul Seligman, Executive Director, U.S. Regulatory Policy, Amgen Inc.

3:50 p.m. **Public Comment Period** (*30 min*)

SESSION V: CONSIDERATIONS ON IMPLEMENTING STRUCTURED APPROACHES TO CHARACTERIZING UNCERTAINTY

Session Objectives:

- Reflecting on the presentations and discussions of the day, identify and discuss possible principles and best practices to successfully implement structured approaches to address uncertainty in the assessment of pharmaceutical benefits and risks.
- Consider the culture and institutional support needed to advance the development, evaluation, and incorporation of structured approaches to evaluate uncertainty in the regulatory decision-making process.

4:20 p.m. Background and Session Objectives (*5 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

4:25 p.m. Reaction Panel and Discussion with the Audience: Decision-Making in the Context of Uncertainty (*35 min.*)

FRANCESCO PIGNATTI
Oncology, Hematology, Diagnostics Section
Scientific and Regulatory Management Department
European Medicines Agency (EMA)

KIMBY BARTON
Director, Bureau of Cardiology, Allergy, and Neurological Sciences
Health Canada

JOHN JENKINS
Director, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

RALPH HORWITZ
Senior Vice President
Clinical Sciences Evaluation
GlaxoSmithKline

TIMOTHY MCDANIELS
Faculty of Science
Institute of Resources and Environment
University of British Columbia

Panel and Discussion Moderator, Baruch Fischhoff, Howard Heinz University Professor, Department of Social and Decision Sciences, Department of Engineering and Public Policy, Carnegie Mellon University

5:00 p.m. Adjourn Day 1

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

February 12–13, 2014

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

---

Day Two

9:00 a.m. Welcome and Reflections from Day 1

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 VI: OVERVIEW OF FDA COMMUNICATION STRATEGIES FOR BENEFIT AND RISK ASSESSMENTS OF PHARMACEUTICALS

Session Objectives:

- Provide an overview of FDA's approach to 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.
- 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.

9:05 a.m. Background and Session Objectives (*5 min.*)

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

9:10 a.m. **What Makes Communicating Uncertainty Difficult for a Regulator?** (*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

9:25 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

9:40 a.m. **What do Patients Really Want to Know about Uncertainty?** (*15 min*.)

K. KIMBERLY MCCLEARY
Director of Strategic Initiatives
FasterCures

9:55 a.m. Discussion with Speakers and Audience (*40 min.*)

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

10:35 a.m. BREAK (*15 min.*)

SESSION VII: 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.
- 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.

10:50 a.m. Background and Session Objectives (*5 min*.)

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

10:55 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

11:10 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

11:25 a.m. **Discussion on Communicating Uncertainty in Benefit and Risk Assessments of Pharmaceutical Products: Tysabri and Beyond** (*1 hr. 25 min.*)

CARMEN BOZIC
Senior Vice President
Clinical and Safety Sciences
Biogen Idec

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

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

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

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

12:50 p.m. LUNCH (50 *min.*)

1:40 p.m. **Public Comment Period** (*30 min.*)

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

Session Objectives:

- Identify and discuss key themes from the workshop.
- Based on workshop presentations and discussions, identify pivotal opportunities to advance more systematic and structured approaches to characterizing and communicating the sources of uncertainty in the assessment of benefits and risks and their implications on pharmaceutical regulatory decisions.
- Identify the input and resources necessary to support the development, evaluation, and incorporation of approaches to evaluate uncertainty in the regulatory decision-making process.
- Identify key gaps in understanding and how best to address those gaps.

2:10 p.m. Closing Discussion with Speakers and Audience: Led by 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

2:20 p.m. **Presentation of Key Themes/Suggested Paths** (*45 min.*)

BRIAN STROM, *Session I Discussion Moderator*
Chancellor, Biomedical and Health Sciences
Rutgers University

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

LISA LAVANGE, *Session III Discussion Moderator*
Director, Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

PAUL SELIGMAN, *Session IV Discussion Moderator*
Executive Director, U.S. Regulatory Policy
Amgen Inc.

BARUCH FISCHHOFF, *Session V Discussion Moderator*
Howard Heinz University Professor
Department of Social and Decision Sciences
Department of Engineering and Public Policy
Carnegie Mellon University

ROBERT RATNER, *Session VI Discussion Moderator*
Chief Scientific and Medical Officer
American Diabetes Association

GAVIN HUNTLEY-FENNER, *Session VII Discussion Moderator*
Human Factors and Safety Consultant
Huntley-Fenner Advisors

3:05 p.m. Reflecting on Tactics and Strategies for A Way Forward: Panel Discussion with Session Chairs, Panelists, and Audience (*35 min.*)

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

3:40 p.m. Adjourn Day 2