Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary

Forum on Drug Discovery, Development, and Translation, Leslie Pray, Rapporteur,

ISBN: 0-309-10739-3, 98 pages, 6 x 9, (2007)

UNDERSTANDING THE BENEFITS AND RISKS OF PHARMACEUTICALS

Workshop Summary

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

Leslie Pray, *Rapporteur*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This study was supported by contracts between the National Academy of Sciences and the Department of Health and Human Services (Contract Nos. 223-01-2460, HHSP233200600500P, HHSP23320042509X1, HHSP2330060043OP, and N01-OD-4-2139), the Department of Veterans Affairs (Contract No. V101(93)P-2136), Abbott Laboratories, American Diabetes Association, American Society for Microbiology, Amgen, Inc., Association of American Medical Colleges, AstraZeneca Pharmaceuticals, Blue Cross Blue Shield Association, Burroughs Wellcome Fund, Doris Duke Charitable Foundation, Eli Lilly and Company, Entelos, Inc., GlaxoSmithKline, Johnson and Johnson, March of Dimes Foundation, Merck and Company, Pfizer, Inc., Schering-Plough Research Institute, and UnitedHealth Group. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-10738-9
International Standard Book Number-10: 0-309-10738-5

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

Suggested citation: Institute of Medicine (IOM). 2007. *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary.* Washington, DC: The National Academies Press.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Gail H. Cassell (Co-Chair), Eli Lilly and Company (1/1/2005–12/31/2008)
Edward W. Holmes (Co-Chair), National University of Singapore (1/1/2005–12/31/2008)
Naomi Aronson, Blue Cross and Blue Shield Association (1/9/2007–12/31/2008)
Leslie Z. Benet, University of California, San Francisco (1/1/2005–12/31/2008)
Nina Bhardwaj, New York University School of Medicine (1/1/2005–9/7/2006)
Catherine Bonuccelli, AstraZeneca Pharmaceuticals (1/9/2007–12/31/2008)
Linda Brady, National Institute of Mental Health (1/9/2007–12/31/2008)
Robert M. Califf, Duke University Medical Center (1/1/2005–12/31/2008)
Scott Campbell, American Diabetes Association (1/1/2005–12/31/2008)
C. Thomas Caskey, University of Texas-Houston Health Science Center (1/1/2005–12/31/2008)
Francis D. Chesley, Jr., Agency for Healthcare Research and Quality (1/9/2007–12/31/2008)
Mark Clanton, National Cancer Institute (1/1/2005–12/31/2006)
Peter Corr, Pfizer Inc. [Retired] (1/9/2007–12/31/2007)
Jeffrey M. Drazen, New England Journal of Medicine (1/1/2005–12/31/2008)
William E. Evans, St. Jude Children's Research Hospital (1/1/2005–12/31/2006)
Joseph M. Feczko, Pfizer Inc. (1/9/2007–12/31/2008)
Wayne Fenton [Deceased], National Institute of Mental Health (1/1/2005–9/3/2006)
Garret A. FitzGerald, University of Pennsylvania School of Medicine (1/1/2005–12/31/2008)
Elaine K. Gallin, The Doris Duke Charitable Foundation (1/1/2005–12/31/2008)
Steven K. Galson, U.S. Food and Drug Administration (1/9/2007–12/31/2008)
Alan M. Garber, Stanford University (1/1/2005–12/31/2007)
Mikhail Gishizky, Entelos, Inc. (1/1/2005–12/31/2008)
Stephen Groft, National Institutes of Health (1/1/2005–12/31/2008)
Carole A. Heilman, National Institute of Allergy and Infectious Diseases (1/1/2005–3/13/2006)

Dale Hu, Centers for Disease Control and Prevention (1/1/2005–12/31/2005)
Michael Katz, March of Dimes Birth Defects Foundation (1/1/2005–12/31/2008)
William F. Keane, Merck & Co., Inc. (1/1/2005–12/31/2008)
Chaitan Khosla, Stanford University (1/1/2005–12/31/2006)
Antonia Kolokathis, Pfizer Inc. (1/1/2005–12/31/2005)
Allan M. Korn, Blue Cross and Blue Shield Association (1/1/2005–12/31/2008)
David Korn, Association of American Medical Colleges (1/1/2005–12/31/2006)
Ronald L. Krall, GlaxoSmithKline (1/9/2007–12/31/2008)
Jeffrey M. Leiden, Clarus Ventures (1/1/2005–12/31/2007) *(at the time of this workshop, Dr. Leiden was representing Abbott Laboratories)*
John M. Leonard, Abbott Laboratories (1/9/2007–12/31/2008)
Nancy Loving, National Coalition for Women with Heart Disease (1/1/2005–6/7/2006)
John R. Marler, National Institute of Neurological Disorders and Stroke (1/1/2005–12/31/2008)
Musa Mayer, AdvancedBC.org (1/1/2005–12/31/2007)
Mark B. McClellan, AEI-Brookings Joint Center for Regulatory Studies (4/2/2007–12/31/2008)
Garry A. Neil, Johnson & Johnson (1/1/2005–12/31/2008)
Joshua J. Ofman, Amgen, Inc. (1/1/2005–12/31/2008)
Susanne Pattee, Cystic Fibrosis Foundation (1/1/2005–12/31/2007)
Cecil B. Pickett, Schering-Plough Research Institute (1/1/2005–12/31/2006)
Joanne L. Rhoads, National Institute of Allergy and Infectious Diseases (1/9/2007–12/31/2008)
Brian Schuster, U.S. Department of Veterans Affairs (1/1/2005–12/31/2006)
B. A. Schwetz, U.S. Department of Health and Human Services (1/1/2005–12/31/2008)
Janet Shoemaker, American Society for Microbiology (1/1/2005–12/31/2008)
Lana Skirboll, National Institutes of Health (1/9/2007–12/31/2008)
Nancy S. Sung, Burroughs Wellcome Fund (1/1/2005–12/31/2008)
James R. Swartz, Stanford University (1/1/2005–12/31/2005)
Reed V. Tuckson, UnitedHealth Group (1/1/2005–12/31/2008)
Sean Tunis, Centers for Medicare and Medicaid Services (1/1/2005–12/31/2006)
Janet Woodcock, U.S. Food and Drug Administration (1/1/2005–12/31/2008)

IOM Staff

Robert B. Giffin, Director (July 2006–present)
Alexander K. Ommaya, Director (January 2005–July 2006)
Adrienne Stith Butler, Senior Program Officer (December 2006–May 2007)
Sally Robinson, Program Officer (December 2006–present)
Heather Begg, Program Associate (January 2005–July 2006)
Andrea Knutsen, Senior Program Assistant (October 2005–present)
Jennifer Rainey, Research Assistant (January 2005–July 2006)

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We wish to thank the following individuals for their review of this report:

Naomi Aronson, Blue Cross Blue Shield Association
Scott Campbell, American Diabetes Association
Steven Galson, U.S. Food and Drug Administration
Jeffrey Leiden, Clarus Ventures

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Bradford Gray**, Editor, Milbank Quarterly and Principal Research Associate, Urban Institute. Appointed by the National Research Council and Institute of Medicine, he was responsible for making certain that an

independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author and the institution.

Contents

Summary*

All pharmaceutical products have inherent risks, and their use involves trade-offs between their therapeutic benefits and their risks. However, the public has a limited understanding of the benefits and risks of drugs, and many individuals believe that drugs approved by the U.S. Food and Drug Administration (FDA) carry no risks. The FDA is responsible for evaluating and balancing the potential risks of drugs with their potential benefits. Assessing, managing, and communicating the benefit–risk profile of a pharmaceutical product is a complex and nuanced scientific, political, and sociological challenge. Once the assessment is made, the FDA is then responsible for managing how to communicate these risks and make healthcare decisions based on them.

To explore these issues, the Forum on Drug Discovery, Development, and Translation conducted a public workshop entitled *Understanding the Benefits and Risks of Pharmaceuticals*, with the broad goals of gaining a better understanding of the current system used to evaluate benefit and risk, and to identify opportunities for improvement. This workshop was held in Washington, D.C., on May 30–31, 2006.

The benefit–risk profiles of pharmaceuticals are constantly evolving as new data are collected throughout the life cycle of a drug. Discussions

*The Forum's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteur as a factual summary of what occurred at the workshop.

during the workshop focused on the following: (1) premarket assessment, during which clinical trial data are used to assess benefit and risk; (2) communication of that information to prescribing physicians and their patients; (3) healthcare decisions made by prescribing physicians and their patients; and (4) the accumulation of benefit–risk information from postmarketing experience, which feeds back into the other phases.

PREMARKET ASSESSMENT

Workshop participants identified several challenges that industry and the FDA must overcome as they make their premarket assessment of pharmaceutical benefit and risk:

- Lack of a systematic, consistent, and transparent approach to benefit–risk analysis;
- Uncertainty regarding how to balance risk and benefits;
- Insufficient knowledge about the risks of drugs at the time of their launch;
- Conflict of interest (for example, experts consult with industry and government on the same products) and involvement of stakeholders (for example, scientists, industry) in evaluating benefit and risk;
- Lack of involvement of prescribing physicians and the public in the FDA regulatory process; and
- Confusing and inconsistent terminology in benefit–risk assessment.

As panelists considered how to construct a systematic, consistent, and transparent approach to benefit–risk analysis, discussion focused on whether and how such a framework should be quantitatively based. Creating a quantitative system has many challenges, including the following:

- Quantitatively capturing a complex drug benefit–risk profile;
- Quantitatively characterizing drug benefit–risk for individuals because of variation among patients in terms of both physiology and preferences;
- Updating benefit–risk assessments with new information through the drug life cycle;
- Addressing the inherent uncertainty in benefit–risk measurement;
- Resolving disagreement about the role that cost should play in benefit–risk calculations;
- Addressing the cost of adopting a quantitative framework and its potential adverse effect on innovation; and
- Effectively presenting and communicating quantitative information (see more below).

Participants discussed the pros and cons of using quality-adjusted life years (QALYs) as a systematic framework for integrating and evaluating the tremendous amount of complex information that must be sifted through in the process of evaluating safety. A proposal was also discussed to adopt a flexible regulatory approach for novel drugs for diseases with large unmet needs. Because safety issues for these drugs are less well-defined and liability risks are higher then usual, the requirements for clinical trials would be modified to include provisional approval for a limited launch to carefully defined physician and patient populations, along with explicit labeling with clear explanations of the known benefits and risks at the time of approval. For the FDA to use such an approach, legislative changes would be required.

COMMUNICATION

The difficulties associated with the communication of benefit and risk information to physicians and patients were discussed extensively. Most of this discussion focused on the challenges involved in physician-to-patient communication, with major challenges including the following:

- Widespread inability, even among well-educated patients, to interpret quantitative information provided about drug benefits and risks;
- Differences in how physicians and patients understand and respond to risk;
- Barriers that make it difficult for physicians to communicate with their patients; and
- Lack of confidence among physicians in their ability to effectively convey quantitative information, compounded by the reality that many physicians themselves are not as well informed as they should be about the benefits and risks of drugs.

Discussion of how to improve communication included a review of recent research on labeling and several calls for the need to better understand the potential usefulness of new ways to visually represent benefit–risk data. The discussion focused on the use of the drug information by patients and clinicians in both product labels and advertising. A proposal for a Prescription Drug Facts Box, modeled after the Nutrition Facts Box for food products, was discussed. The transformation of drug labels currently under way at the FDA was also described.

HEALTHCARE DECISION MAKING

An overarching theme of the workshop discussion was that the ultimate goal of improving benefit–risk assessment and communication is to enable "better" healthcare decision making. Rarely do ordinary individuals explicitly calculate benefit–risk trade-offs when making a decision. Most patients make on-the-spot, experiential decisions that are influenced by a complicated set of interacting factors that were described by the presenters, including the following:

- Patients' inability to understand quantitative information (innumeracy);
- Patient assumptions about benefit and risk (for example, automatically associating high benefit with low risk);
- Whether or not the prescribing physician has voiced his or her opinion;
- How information on drug benefits and risks is presented to the patient;
- Nature of the patient's condition; and
- Patients' tolerance of uncertainty.

Many contextual factors influence healthcare decision making; therefore improving the process is difficult. Many participants suggested that patient education regarding understanding pharmaceutical benefit and risk concepts was paramount, thus they should be more involved with the decision-making process.

There was substantial debate on the FDA's responsibility for guiding decision making. While some participants favored a more active FDA role in guiding decisions, others argued for an approach in which physicians and patients are given information with which to make their own, informed judgments.

ACCUMULATION OF BENEFIT–RISK INFORMATION FROM POSTMARKETING EXPERIENCE

At the time of approval, the benefit–risk profile of a typical drug is not fully understood. It is only after approval and widespread use that the profile will become fully understood. Ideally, this information would be used to update extant benefit–risk profiles. However, the limited capacity of the postmarketing surveillance system to acquire this information and use it to update the benefit–risk profiles of drugs on the market was documented and discussed extensively. Some workshop participants described the postmarketing safety data system as a "failure." Major weaknesses in the current system, as identified during the meeting, included inadequate

data collection, methodological difficulties associated with detecting adverse drug events, and the lack of standardized approaches to coding and collecting data from multiple sources. While mining postmarketing information may generate better hypotheses about benefit and risk, some participants argued that this cannot replace controlled studies refining our understanding of drug benefits and risks over time.

NEXT STEPS

Several themes emerged from discussions at the workshop:

- It is important in pharmaceutical benefit–risk analysis to provide patients and physicians with the best possible information for making informed decisions about the use of pharmaceuticals.
- It is important to employ quantitative and standardized approaches when trying to evaluate pharmaceutical benefit–risk. These approaches should augment rather than replace current regulatory approaches to pharmaceutical approval and labeling. More work needs to be done to develop and validate such tools.
- It is important to educate patients and physicians about the concepts of pharmaceutical benefit–risk and how these are assessed throughout the life cycle of a drug.
- It is important to develop and validate improved tools for communicating pharmaceutical benefit–risk information to patients and physicians.
- It is important to involve patients and physicians in the development of new tools for evaluating and communicating data concerning pharmaceutical benefit–risk.
- It is important to improve the current system for collecting postmarketing safety and efficacy data on marketed pharmaceuticals.

The workshop concluded with a discussion of possible next steps. There was general agreement that one or more pilot studies should be designed, in conjunction with the FDA, to address some of the suggestions discussed during the workshop, such as quantifying benefit–risk assessment through the use of QALYs and using a Prescription Drug Facts Box to better communicate drug information to patients and clinicians. Additional suggestions included developing a fact sheet to help educate the public about the benefits and risks of drugs, planning follow-up meetings to focus on specific issues, encouraging patient and community physician involvement in future discussions, incorporating costs in the discussion of benefit–risk analysis, and instituting citizen councils to involve the public in decisions made by the FDA regarding drug benefits

and risks. Individually, participants suggested the following initiatives for moving forward:

- Develop an eight- to ten-page bulleted summary of facts and assumptions about pharmaceutical risk and benefit that the IOM or the Forum could use to educate legislators and others. This could also be posted on the web for physicians and patients.
- Design one or more pilot studies with the FDA to address some of the suggestions and considerations voiced at this meeting—for example, a study on utility-based analysis of benefit–risk for either an existing drug or a drug that is under FDA consideration. A second pilot could test the utility of one or more new patient–physician communication tools such as the Prescription Drug Facts Box. Adopting an experimental attitude would be a way to move forward several of the specific initiatives suggested by meeting participants.
- Plan follow-up meetings that focus on specific problems. For example, one meeting could address novel approaches to postmarketing surveillance and the limits of the FDA's Adverse Event Reporting System, another might compare different quantitative tools for evaluating drug benefit–risk, and a third might address risk management plans and whether and how they should be submitted at the time of a new drug application.
- Encourage patient and physician involvement in future discussions.
- Incorporate pharmaceutical pricing in the discussion of benefit–risk analysis because, at least for legislators, cost is a critical element of the discussion.
- Avoid assigning blame among the various stakeholders involved in benefit–risk assessment because it damages the public trust.
- Consider instituting citizen councils, as the United Kingdom's National Institute for Clinical Excellence did when faced with a similar crisis in public trust. Decisions to be made by the FDA regarding benefit–risk assessment could be laid out for the councils, who would then be asked how they value the options. Not only would this tactic add legitimacy to the decisions being made, council members could become champions for those decisions—and "the state of the science"—in the larger community.

Several participants suggested that there is a need for urgency in addressing these steps because of the imminent reauthorization of the Prescription Drug User Fee Act (PDUFA) and the possible enactment of other drug safety bills.

1

Introduction

Throughout its 100-year history,[1] the U.S. Food and Drug Administration (FDA) has sought to protect the public's health by "assuring that safe and effective drugs are available to the American people" (FDA 2007). Over time, a large segment of the public has developed the belief that FDA- approved drugs carry no risk.[2] Yet all drugs have inherent risks[3] and one of the functions of the FDA is to evaluate and balance these potential risks against potential benefits. Assessing and managing the risks of modern medical products is a complex and nuanced scientific, political, and sociological challenge that includes not only the assessment of risks and benefits, but also how we communicate them and make healthcare decisions based on them.

To explore these issues, the Forum on Drug Discovery, Development, and Translation conducted a public workshop entitled *Understanding the Benefits and Risks of Pharmaceuticals*, with the broad goals of gaining a better understanding of the current system for evaluating benefit and risk and of identifying opportunities for improvement. This workshop was held in Washington, D.C., on May 30–31, 2006.

[1]The FDA originated in June 1906, when President Teddy Roosevelt signed the Food and Drugs Act, entrusting its implementation to the U.S. Department of Agriculture's Bureau of Chemistry. The bureau eventually became the FDA.

[2]This section is based largely on introductory comments by workshop co-chairs Steven Galson, FDA and Jeff Leiden, Abbott Laboratories.

[3]The FDA defines a safe product as "one with reasonable risks given the magnitude of the expected benefit and the available alternatives."

The benefit–risk profiles of pharmaceuticals are constantly evolving as new data are collected throughout the life cycle of a drug. Discussions during the workshop focused on the following: (1) premarket assessment by the FDA and/or industry, during which clinical trial data are used to assess benefit and risk; (2) communication of that information to prescribing physicians and their patients; (3) healthcare decisions made by prescribing physicians and their patients; and (4) the accumulation of benefit–risk information from postmarketing experience, which feeds back into the other phases (Figure 1-1).

The workshop considered the role of multiple stakeholders in benefit–risk assessment throughout the development process, including the FDA, a key player in benefit–risk analyses and decision making; academia, where much of the early discovery takes place; industry, where most of the development process occurs and where marketing plays an ever-increasing role in benefit–risk communication; and physicians and patients, where final decisions about drug use are made.

This workshop summary is organized into 6 sections. Section 2 focuses on the regulatory assessment phase of the benefit–risk assessment process. It identifies challenges and potential solutions in premarket assessment of benefits and risks, including approaches to evaluating drug safety. It also examines methods used by other industries for assessing benefits and risks. Section 3 addresses communication issues such as how to quantitatively communicate information about risk to the public, and possible solutions for providing user-friendly information to physicians and patients. Section 4 focuses on healthcare decision making by providers and patients. It discusses how individuals acquire information and make judgments about benefits and risks, how decisions depend on subtle contextual factors, and ways to help patients make informed decisions. Section 5 discusses patient experience with drugs over time and the limitations of postmarketing surveillance. Section 6 concludes with actionable next steps identified by workshop participants.

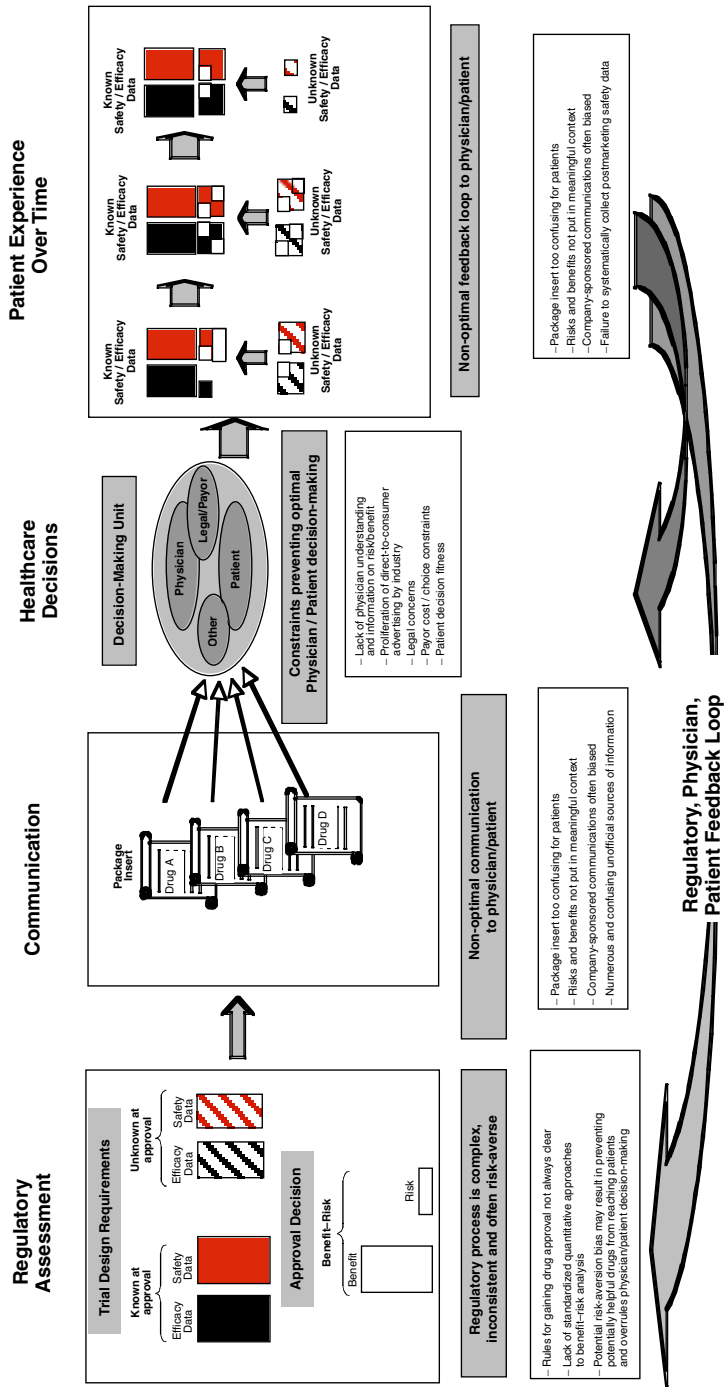

FIGURE 1-1 Constraints and limitations of the four-part life cycle of the pharmaceutical drug benefit–risk assessment process.
SOURCE: Adapted from Jeffrey Leiden's presentation.

2

Regulatory Assessment

This section summarizes the presentations and discussions regarding the benefit–risk assessment that occurs in the premarket regulatory phase. Participants' discussion focused on the value of formal benefit–risk assessment and the best ways to conduct it, while also considering the public perception of the benefit–risk assessment process.

PROBLEMS AND POTENTIAL SOLUTIONS FOR REGULATORY ASSESSMENT OF BENEFIT AND RISK[1]

Panelists discussed how benefit and risk data are currently collected and evaluated prior to a drug gaining regulatory approval from the FDA. The challenges to completing the assessment were identified as follows:

- Lack of a systematic, consistent, and transparent approach to benefit–risk analysis;
- Uncertainty regarding how to balance risk and benefit;
- Insufficient knowledge about the risks of drugs at the time of their launch;
- Conflict of interest (for example, experts consult with industry and

[1]This section is based on the presentations of Peter Tollman,The Boston Consulting Group; Louis Garrison, University of Washington; Alan Garber, Stanford University; Steven Galson, FDA; David Slavin, Pfizer; Larry Lesko, FDA; Brian Strom, University of Pennsylvania; Douglas Throckmorton, FDA; and Jeffrey Leiden, Abbott Laboratories.

government on the same products) and involvement of stakeholders (for example, scientists, industry) in evaluating benefit and risk;

- Lack of involvement of prescribing physicians and the public in the FDA regulatory process; and
- Confusing and inconsistent terminology in benefit–risk assessment.

Value of a Quantitative Approach to Benefit–Risk Assessment

Dr. Tollman explained that federal agencies, such as the Environmental Protection Agency (EPA) and the Federal Motor Carrier Safety Administration (FMCSA) use quantitative evaluations to more rigorously assess benefit and risk, as well as cost. While parallels to pharmaceuticals are not conclusive, they suggest that quantitative approaches to drug benefit–risk assessment may be viable. Quantification, however, has its own set of challenges:

- Quantitatively capturing a complex drug benefit–risk profile;
- Quantitatively characterizing drug benefit–risk for individuals because of variation among patients in terms of both physiology and preferences;
- Updating benefit–risk assessments with new information through the drug life cycle;
- Addressing the inherent uncertainty in benefit–risk measurement;
- Addressing disagreement about the role that cost should play in benefit–risk calculations;
- Addressing the cost of adopting a quantitative framework and its potential adverse effect on innovation; and
- Effectively presenting and communicating quantitative information.

Dr. Tollman suggested that adopting a quantitative approach could be beneficial in that it could objectively combine clinical trial data and information on patient preferences. Dr. Tollman noted that the academic community has a number of simple, powerful frameworks and utility weighting methods that could feasibly be adapted to the drug approval process. He cautioned, however, against quantitative elements being too simplistically or narrowly interpreted.

Dr. Tollman further argued that a more structured, transparent, and quantitative approach would be advantageous for all constituents—patients, regulators, and industry. For patients, advantages include the fact that the approval decision incorporates patient preferences, ultimate drug choice is based on individual response and preferences, and more differentiated treatment options become available to patients. For regulators, advantages include decisions that are grounded in a preagreed

framework that is consistently maintained from year to year and across divisions of the FDA. For industry, advantages include more predictable results and ultimately less attrition, more opportunities to innovate and differentiate products, and an ability to better align internal portfolio planning with a drug candidate's true likelihood of success.

Challenges in Developing a Common Methodology

Dr. Galson argued that developing a common methodology for assessing efficacy and safety throughout the regulatory life cycle of a drug poses an enormous challenge because our understanding can change substantially over its course. While knowledge about efficacy grows exponentially during clinical testing, it continues to increase after approval when drugs are put to new uses. Also, exponential growth in our knowledge of safety doesn't occur until after the drug has reached the market, when sample size increases and more data become available (Figure 2-1).

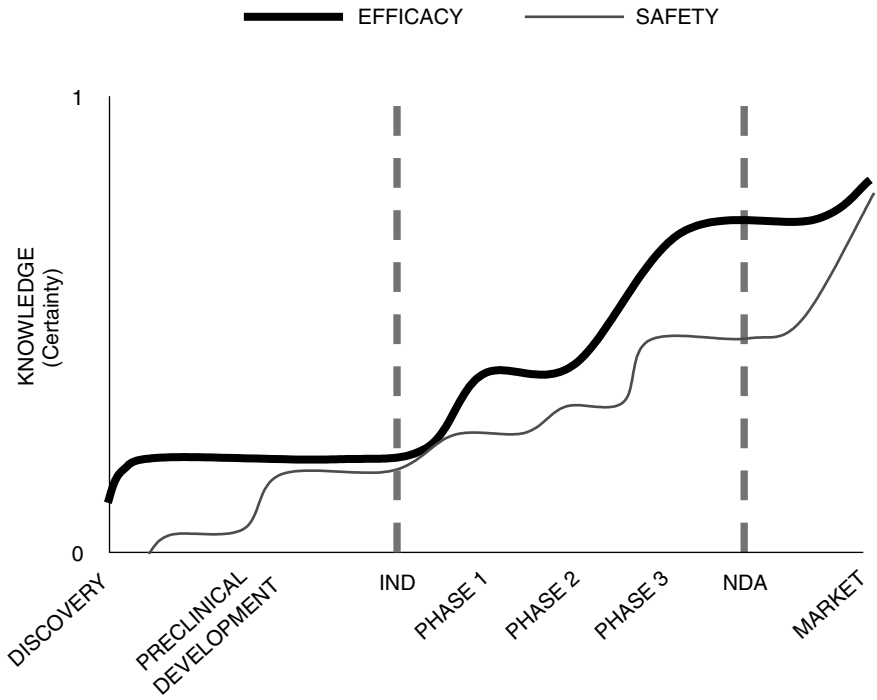

FIGURE 2-1 The time paths of knowledge related to drug efficacy and drug safety through the drug development process.
SOURCE: Adapted from Steven Galson's presentation.

Dr. Galson used the FDA's experience with Lotronex, a serotonin receptor antagonist indicated for treatment of irritable bowel syndrome, to illustrate how the use pattern of an approved drug may change after clinical trials and how our assumptions about risk change over time. The premarketing safety database, which included approximately 3,000 patients in two dose-ranging trials, revealed only limited dose-dependent adverse events. After launch, however, when the population of patients who were exposed to the drug increased rapidly, there was a severe increase in labeled gastrointestinal (GI) events. The drug was withdrawn, the clinical trial data were reassessed, and a relaunch was initiated after the implementation of a risk management plan. Dr. Galson argued that the misprescribing of Lotronex suggests that even the strongest predictive benefit–risk methodology can be defeated by knowledge gaps in the development program. Even if a common methodology for assessing benefit–risk ratios is developed, he noted, communication strategies for rollout and proper drug use must also be improved.

Dr. Galson further noted the lack of unanimity about the ideal benefit–risk balance for therapeutic products—there is still no consensus about what a good benefit–risk ratio is. While the FDA's responsibility is to evaluate the benefits and risks of a drug for the population at large (or for the population for which the drug is being developed), providers are responsible for balancing benefits and risks for individual patients, and patients are responsible for making final benefit–risk decisions based on their own information and values (Figure 2-2).

Dr. Galson emphasized that drug safety is a societal issue, and the best benefit–risk assessment methodology will take us only so far. He presented two case examples to illustrate the societal context of the problem. First, the American Psychiatric Association harshly criticized FDA efforts to improve the labeling of SSRI (selective serotonin reuptake inhibitor) antidepressants, arguing that the increased level of warning and the better description of benefit and risk may scare away patients who could benefit from the drug. Dr. Galson remarked that it is difficult to see how improving benefit–risk assessment methodology will resolve this type of challenge.

As a second example, although the FDA has implemented several risk management plans to make sure that pregnant women do not take Accutane, the FDA still receives e-mails arguing that even one congenital malformation is not worth the benefits of this cosmetic drug. He suggests that no amount of benefit–risk assessment methodology can resolve this conflict. He concluded by stating that while the challenge in balancing pharmaceutical product benefit and risk is multidisciplinary, successful adoption of methodological improvements would nonetheless benefit all stakeholders.

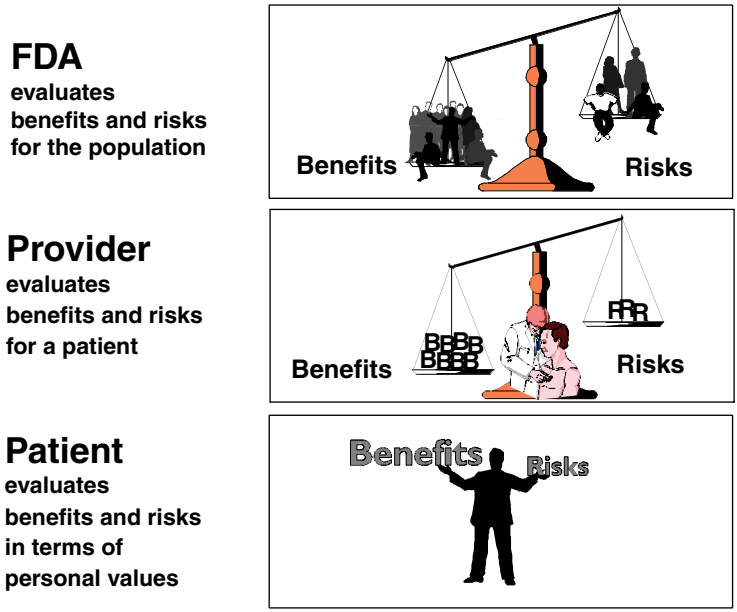

FIGURE 2-2 Alternative perspectives on the benefit–risk relationship.
SOURCE: Adapted from Steven Galson's presentation.

QUANTITATIVE APPROACHES

A QALY-Based Approach to Benefit–Risk Modeling

Committees often take a piecemeal approach when weighing benefit and risk evidence and making approval decisions. Dr. Garrison suggested that it would be useful to have a more systematic framework for integrating and evaluating the tremendous amount of complex information that must be sifted in the process of evaluating safety. He commented on how pharmaceutical benefits and risks are measured in different units and how there is no clear approach for their quantification. He suggested that a more transparent, structured model based on quality-adjusted life years (QALYs)[2] could be a basis for developing that framework.

[2]Quality-adjusted life years (QALYs) are a method of quantifying the benefit of a medical intervention which accounts for both quantity and quality of life. Perfect health for a year is assigned a value of 1; death is assigned a value of 0. For each extra year lived if a person is not in full health—for example, if a person is bedridden, in a wheelchair, has lost a limb, etc.—they are given a value between 0 and 1 for each of the remaining years of their life.

There is general consensus, he argued, that QALYs are a useful tool. Health technology assessment (HTA) and health outcomes researchers express health effects in terms of QALYs, and a recent Institute of Medicine (IOM) panel recommended that regulatory cost-effectiveness analyses (CEAs) use QALYs to represent net health effects (IOM 2006). However, it must be decided whether QALY-based utility analysis and other outcomes research tools (e.g., integrative modeling of long-term health outcomes) provide a useful methodology for a more formal, explicit, transparent, and quantitative process for assessing pharmaceutical drug benefit–risk than the current approach.

Dr. Garrison explained that for most new drugs, estimating QALYs requires using models to synthesize information and extrapolate beyond what is traditionally collected in Phase III trials. While this method is being applied across a wide spectrum of diseases, usually for purposes of reimbursement, it has limits. He asserted that the FDA and physicians either do not fully understand the method, or do not believe that it is scientifically valid; it may be inappropriate for physicians to use the method at their level of decision making; it is usually applied more to benefits than to adverse events (risks); and QALYs are risk-neutral and do not explicitly take into account risk aversions (although there are ways to adjust for this).

Dr. Garrison noted the importance of including subgroup analyses and calculating benefit–risk ratios separately for different populations. He also noted two key challenges of measuring risk in terms of QALYs. First, clinical trial signals are often weak, making it difficult to measure known adverse events in quality terms without making certain assumptions. Second, it is difficult to measure the potentially serious side effects that occur at rates of less than 1 in 10,000 or 1 in 100,000.

Dr. Garrison recommended that the feasibility and usefulness of an explicit, transparent process of benefit–risk measurement relying on QALY-based outcome models be more fully evaluated, with the recognition that it may not be reasonable to apply the full methodology to every product and that patient preferences vary.

Patient Differences

Dr. Garber outlined the difficulties of creating a single measure that sums up benefits and risks. Not only does every drug have multiple health effects, but people perceive these effects differently. Patient differences pose a tremendous challenge for benefit–risk assessment. Dr. Garber identified two types of patient heterogeneity: physiological (e.g., genetic variation) and preference variation (different people attaching different values to risks and benefits). He remarked that no federal agency has a formal process for weighing preference variation, and there is no consen-

sus in the literature for how it should be done. He explained the impossibility of relying on a purely objective framework "that is independent of patient preferences or some kind of element of human judgment" and discussed problems that can arise when decisions are based on population averages rather than patient preferences. The challenges will increase as we deal more frequently with treatments whose effects are not only life extension, but also improvement in function or quality of life.

Dr. Garber suggested that some variables in a cost-effectiveness analysis might also be important to include in a more general analysis. He discussed the results of a study published in 2003, before Vioxx was withdrawn, of cyclooxygenase-2 (COX-2) inhibitors versus naproxen, and explained how that study demonstrates the usefulness of QALYs as a metric (Speigel et al. 2003). The study makes it very clear that what can be a "bad" drug for some people (people not at risk of GI bleeding) can be a very "good" drug for others (people at risk of GI bleeding). He remarked that the types of information that would be needed for a preference-based benefit–risk analysis are not very demanding, compared to what has historically been required for FDA approval.

Participants noted that the calculation of QALYs requires modeling and extrapolation beyond the information typically collected in Phase III trials. Since modeling requires making assumptions—for example, how surrogate outcomes translate into clinical benefit—the uncertainty surrounding those assumptions must be addressed. Dr. Garber argued that while addressing these uncertainties complicates such models, the alternatives are almost invariably worse. Recommendations based on one-year outcomes in a clinical trial often reflect a range of informal assumptions about what is going to happen beyond the end of the trial. A formal model, on the other hand, requires that assumptions be explicit and transparent.

Additional questions on uncertainty were discussed. For example, given that there are different levels of uncertainty in benefits and risks across disease areas, what should drug companies have to achieve at the end of Phase III, and might it be more than just a certain benefit-minus-harm difference? Could it instead be a commitment to do Phase IV studies or to spend a certain amount to reduce uncertainty about risks and benefits? Is it worth spending $10 million or $20 million to narrow the confidence interval (that is, uncertainty) about risks and benefits only slightly, and when might this greater certainty suggest that an approval decision be changed?

While discussing variability among subgroups and individual patients, a participant noted that the balance of risks and benefits may be specific to particular populations, and that unless you can identify such populations, the effort to assess risks and benefits breaks down. Accurately identifying such populations involves significant physician

involvement, over which the FDA has little control. While the FDA can define benefits and risks for different populations, it cannot prevent the inappropriate prescribing by physicians once a drug is on the market. Dr. Garber remarked that while it is inappropriate for a regulatory agency to be a source for improving physician practice, sometimes there comes a point where the likelihood of misuse is so great that it does change the FDA's thinking about approval.

Other Ways to Think About Risk

Dr. Slavin introduced the notion of tolerability of risk (TOR), which he noted is widely used in evaluating occupational and environmental standards in both the United States and Europe. It is particularly useful in situations where the incidence of the risks is unknown and the understanding of the hazards are ambiguous. Rather than generating a single number for comparison against a standard (because there is insufficient knowledge for true certainty), a TOR framework describes a pre-agreed, bounded area of risk, or a box, against which a probabilistically derived footprint of the true risk can be compared. Over time, as more data are collected and knowledge increases, the area of that footprint shrinks, and any decisions that need to be made about a drug become easier to make.

Quantitative Assessment of Pre-Approval Risk: Zometa as a Case Example

Dr. Lesko argued that quantitative tools are attractive because they are complementary to conventional tools, which have certain limitations. For example, when Phase III data are analyzed with conventional tools, the change in response from baseline to end of study is compared between treatment and placebo groups. Measurement of response to treatment between baseline and end of study are not always considered in conventional studies, even though they are often the most interesting since they reflect disease progression or treatment over time. Quantitative analyses allow us to look at those measurements. Also, most Phase III conventional data analyses treat doses as categorical, not continuous, variables.

Dr. Lesko presented a case study on Zometa, a drug indicated for the treatment of hypercalcemia of malignancy and also for multiple myeloma and bone metathesis from solid tumors. The initial review was conducted by the FDA's Office of Clinical Pharmacology with input from the Pharmacometrics Team (quantitative clinical pharmacology). For Zometa, the safety endpoint was renal toxicity. Dr. Lesko demonstrated how the use of quantitative tools revealed more accurate information about risk. Examining the difference between placebo and Zometa

categorically—normal versus abnormal renal function—was misleading in terms of the risk for any given patient of developing renal deterioration. Postmarketing reports began to reveal that the drug was associated with renal deterioration when used in a wider population than was defined in the clinical trial population. Quantitative tools were then employed to examine renal deterioration by using creatinine clearance (an indication of renal deterioration, which in turn is a predictor of renal toxicity risk) as a continuous variable.

Through data obtained from multiple quantitative analyses, Dr. Lesko and his team learned that a patient's baseline renal functioning affected their risk of renal deterioration. They gained a better understanding of the drug's toxicity and were able to inform the warning section and dosing recommendation on the product label. They decided to select doses of Zometa according to baseline creatinine clearance. It was demonstrated through quantitative analysis that linking kidney function exposure and dose adjustment would provide a reduction in the risk in individual patients and subgroups of patient.

While the learning process with Zometa was not used to design additional clinical trials (via simulations), this did occur with some of the other case examples that the Pharmacometrics Team has studied. In conclusion, Dr. Lesko argued that although there are some risks that we can do nothing about (e.g., age), others can be addressed and reduced through the use of quantitative analyses of treatment data.

Dr. Lesko first discussed the "learn–confirm paradigm" (Sheiner 1997) for delivering news to patients about benefits and risks. This construct separates drug development into two sets of concepts: (1) Learn—benefit–risk is not well defined and is assessed by looking across all of the clinical data for such things as dose-response and variables that influence exposure and its relationship to toxicity (he reported that the set of quantitative tools used in the case of Zometa were associated with the learning aspect of drug development); and (2) Confirm—efficacy is well defined, and rigorous, randomized control trials using pre-specified statistical analyses have been designed to answer efficacy (yes or no) questions in a general population.

An Argument Against Benefit–Risk Analysis in Drug Approval

Dr. Strom argued that quantitative benefit–risk ratios should not be used to make drug approval decisions, citing the following reasons:

- Understanding of the benefit and risk relationship will change throughout the life of a drug and may vary between individual patients or populations.

- Many important qualitative variables would not be adequately addressed—for example, marketing practices, prescribing patterns, patient compliance when taking the drug, and experimental design.
- Despite decades of effort, assessment of a drug's benefits presents enormous challenges—for example, quantifying pain and comparing unrelated outcomes, such as pain and heart attack or gastrointestinal bleed.
- Measuring risks often requires the use of surrogate measures because we can't wait for the ultimate outcome.
- Benefits and risks are measured in different units and vary by context, for example: How many patients with pain relief (the benefit) are needed to balance one heart attack (the risk)? How much short-term risk is acceptable for long-term benefit (e.g., statins and blood pressure medications that yield long-term benefit)? How much individual risk is acceptable for societal benefit (e.g., vaccines)? How much societal risk is acceptable for individual benefit (e.g., antibiotics)?

Dr. Strom argued that plugging benefit and risk measures into a single equation is not feasible. While other speakers suggested standardizing units using a measure of utility, he argued that utility is a subjective judgment that varies among individuals. He questioned the practice of imposing average subjective judgment on individuals. He reasoned that, given such wide variation, the decision should be made by the person needing the benefit and taking the risk.

In conclusion, Dr. Strom remarked that subjective judgments are being made throughout the entire benefit–risk assessment life cycle and it is naïve to think that we can quantify these subjective judgments. Pharmaceutical companies make subjective judgments about whether to develop a drug; advisory boards and regulators make subjective judgments about whether to approve a drug; physicians make subjective judgments about whether to prescribe a drug; and patients make subjective judgments about whether to take a drug. The current system is flawed by its subjectivity, but it is probably the best there is. He cautioned that we risk forcing wrong answers by being overly quantitative and precise.

Dr. Strom's recommendation that benefit–risk assessment not be quantified elicited much discussion. Dr. Leiden elaborated on two reasons for quantification. First, he reported that some lower-level reviewers in the FDA told him they feel pressure to not make mistakes. A more standardized, quantitative system would give FDA reviewers ammunition to explain their decisions to legislators and to change their decisions if the data suggest that they should. Second, there is tremendous anxiety in pharmaceutical companies trying to understand what it is that the FDA wants. Part of this anxiety stems from different expectations among divi-

sions within the agency and sometimes even among reviewers within divisions. Having more standardized, quantifiable methods would encourage industry to pursue innovative drug development programs that they might not otherwise pursue. Dr. Leiden remarked that the system is "moving in the wrong direction . . . of squashing innovation further." Others agreed that the fear-based push for larger clinical samples sizes is leading to "an overly conservative system."

Dr. Tollman argued that using a formula to assess benefit and risk may create false precision. On the other hand, to the extent that there is quantitative information and a valid statistical analysis of the benefits and risks of a drug that he is considering, he as a patient would like to see it. Finding a way to present the quantitative information in a way that would be helpful for patients would be very valuable. He said, "It would help me inform my choice, and from my point of view, that's the overall objective of the process."

Implementing Benefit–Risk Assessment

Dr. Throckmorton argued that integrating quantitative benefit–risk assessment into the early drug development process would enable all stakeholders to make better decisions. Companies could make earlier and more informed go or no-go decisions, the FDA and other regulators could make more informed early approval decisions, and patients could make better decisions about treatment options. He made three assertions regarding the development of a better approach to benefit–risk assessment:

First, benefit–risk assessment must be patient-centered, providing the best possible information to patients so that they can make the best possible choices.

Second, benefit–risk assessment must be integrated into the drug development process without reducing either safety or efficacy standards. Dr. Throckmorton proposed utilization of "model-based drug development" as a platform for achieving this. He noted that it would allow easy updating of benefit–risk assessments as new data become available. He also emphasized the importance of early dialogue between pharmaceutical companies and the FDA. Early discussion and agreement may provide regulatory clarity and reduce sponsor uncertainty, thereby resulting in more efficient product development. This requires that all assumptions and uncertainties are openly stated and discussed.

Third, a successful benefit–risk analysis must rely on standards. While there is no one-size-fits-all methodology, we need to identify and adopt best practices and build greater familiarity and expertise within the regulatory agencies and also in industry and academia. The Voluntary Genomics Data Submissions mechanism, whereby sponsors provide

genomic information for nonregulatory, data-sharing discussions, could serve as a model for facilitating this kind of information exchange.

Dr. Throckmorton identified key first steps in the implementation of this type of a system, analysis and application. Analysis should include some examples, ideally from prospective use during drug development. An analysis of nuanced benefit–risk decisions that have been made in the past would also be informative (e.g., drugs that may not have been lifesaving but had symptomatic benefits). Analysis could assist in developing appropriate methodologies for evaluating risk and benefit data. Then, these methodologies need to be applied and integrated into early drug development. Ideally, drug developers would propose what they believe to be the best assessment of risk and benefit, and regulators would have the expertise to discuss this assessment in a meaningful, forward-thinking way.

Flexibility for Products That Address Large Unmet Need

Dr. Leiden emphasized that it would be tremendously beneficial to biotech and pharmaceutical companies to have a clear understanding early on regarding the FDA's efficacy and safety requirements, particularly for diseases with large unmet need where the lack of a clear regulatory path discourages companies from proceeding. Novel drugs for diseases with large unmet need have less well-defined regulatory paths, longer development times, less well-defined and often smaller markets, less well-defined safety issues, and high liability risks. These challenges make pharmaceutical executives more reluctant to initiate clinical development programs for novel drugs. Further, they create a much lower threshold for halting programs when the first hint of a safety or efficacy problem surfaces. Dr. Leiden proposed flexible regulatory, intellectual property (IP), and liability approaches for these products. This would require several steps: agreeing on a predefined list of high-priority diseases with large unmet need; significantly modifying the requirements for clinical trials for such agents (e.g., strong Phase I signals allowing for fast transition to Phase II–III with relatively small numbers of patients); offering provisional approval; offering a designated period of market exclusivity, so that the company is guaranteed minimum market time no matter how long development takes; and reduced liability exposure.

Dr. Leiden proposed that in exchange, pharmaceutical companies would agree to pursue a limited launch of products that obtained such a provisional approval. This would involve a limited launch to a carefully defined physician and patient population; explicit labeling with clear explanations of the known benefits and risks at the time of approval; limited marketing and promotion, with no direct-to-consumer or journal advertis-

ing; and prospectively defined Phase IV requirements. Dr. Leiden suggested that only after successfully completing Phase IV trials should companies be allowed to expand their marketing efforts and broaden their launch.

Dr. Leiden argued that both patients and industry would benefit from a flexible system as described above. Patients would benefit from: 1) the availability of more novel medicines for diseases with unmet need, 2) more drugs for less-prevalent diseases, and 3) a better understanding of benefits and risks made possible by the extensive efficacy and safety data collection in Phase IV. Industry would benefit from the incentive to pursue innovative products for smaller markets (for example, by not spending $100 million or $200 million on products that would be too risky and expensive to push through the regulatory process); guaranteed market exclusivity; and further R&D made possible by the revenue from provisionally approved products.

Dr. Leiden noted that his proposed system may sound heretical, given so much focus on the risks incurred because of the limits of what we know from testing a drug on only a few thousand patients. Here, he is advocating testing drugs in even fewer patients. He pointed to HIV/AIDS as a successful example of this kind of system having worked in the past. In the early and mid-1990s, patient advocacy groups pushed pharmaceutical companies and the FDA for early access to new treatments. FDA responded by allowing and establishing expedited review, with the first HIV/AIDS drugs being approved less than four years after the initial discovery. Not only did HIV/AIDS evolve from a fatal to a chronic illness in less than 10 years, at least in regions of the world where access to drugs is unlimited, but there have been no product withdrawals due to unexpected safety issues. Dr. Leiden stated that if the current system is not improved, "we will essentially strangle innovation, at least from large pharmaceutical companies."

There was some question about how difficult it would be to adopt "model-based drug development" as a platform for integrating additional data into the development process, as Dr. Throckmorton proposed, and whether these data would add much value. Dr. Throckmorton responded that his point was that if we limit ourselves to only some aspect of the data and do not use all of the available information—if sponsors do not communicate about the animal models, biomarkers, internal benefit–risk decision making, or other tools that they are using—then we risk losing a chance to understand how decisions are being made. He argued that open communication about choices being made provides clarity and understanding and has value in and of itself.

Dr. Leiden agreed with Dr. Throckmorton's concern and noted that the end-of-Phase II(A) meetings that the FDA has begun offering have been tremendously beneficial to industry and have opened up a whole

new avenue of discussion at a time when critical decisions are being made about very expensive Phase II(B) and III programs. That kind of interaction is extremely helpful not just to the FDA but also to industry, providing clarity and transparency. He also commented on a notion that Dr. Throckmorton addressed in his presentation: that we can explore some of these new benefit–risk methodologies in a penalty-free way (without adversely impacting approval of the drug), as was done with pharmacogenomic information before the FDA really understood how that information was going to influence regulatory approval. It would allow us to put a database together and gain a better understanding of how to use benefit–risk information.

The discussion turned to uncertainty. Dr. Throckmorton's suggestion that benefit–risk data be used in clinical trial simulation early during development raised questions about how the uncertainty surrounding unknown risks would be handled. Dr. Throckmorton agreed that while we know very little about safety until later in development, class effects could be extrapolated and used to find safety signals.

Dr. Leiden argued that the proposal he put forward begins to address the issue of uncertainty. For example, there is a very explicit hypothesis about the unique benefits of COX-2s with respect to decreasing GI bleeding, but the cardiovascular risk signals during Phase I, II, or III were not recognized. Had Vioxx been developed according to the paradigm that he suggested, the drug would have been rolled out only to those patients with arthritis who were at risk of GI bleeding. It would not have been until prospective Phase IV studies were initiated that we would have begun to look at the potential benefit in other patients. That is where we would have seen the safety signal—while the drugs were still restricted with respect to being prescribed only to patients for whom the benefit–risk ratio was known to be favorable. He argued that had this route been taken, Vioxx would still be on the market and available for those patients. For many other drugs as well, the majority of side effects are not going to show a signal during Phase I, II, or III.

When asked to comment on Dr. Leiden's proposal for change, Dr. Throckmorton noted that some components of Dr. Leiden's proposal are things that the FDA is already doing but perhaps could be doing more consistently or better. Other components would require changes in regulatory law. We need to determine which parts of the process would add the most value if improved—and which parts are not being addressed—in order to decide how to move forward.

Dr. Goldman[3] said that she was intrigued by Dr. Leiden's proposal and noted that although the EPA created a fast-track process for reduced-

[3]Lynn Goldman, Johns Hopkins University.

risk pesticides, it was not easy and it required a lot of work with companies and other stakeholders. Congress eventually adopted it and put legislation in place that strengthened it considerably. She suggested that the FDA could pursue a similar path in a step-by-step fashion.

LESSONS FROM OTHER INDUSTRIES[4]

Two of the workshop sessions focused on lessons to be learned from other industries. The first session, "Assessing the Effectiveness of Risk–Benefit Algorithms from Other Industries," focused on the methodologies used to evaluate benefit–risk ratios of various nonpharmaceutical products. The content of that session is summarized here.

Lessons Learned from Chemical Risk Assessment

Dr. Paustenbach highlighted key developments in the history of chemical risk assessment, including the 1983 publication of the "Red Book" (National Research Council 1983). The anticipated role of the Red Book was that it would provide a framework for a well-integrated risk-assessment process that could quantitatively characterize chemical hazards in a way that was objective and "separate and distinct" from decision making. While the field has realized some of that early optimism and risk assessment has become integrated into most regulatory guidance and policy involving chemicals, there have been some shortcomings. (For example, Dr. Jasanoff[5] argued that experience and social science research have shown that risk assessment is limited by uncertainty and ignorance, and the boundary line between where science [risk assessment] ends and policy [risk management] begins is not as clear-cut as we sometimes believe.)

Dr. Paustenbach identified 10 lessons from chemical risk assessment that may be relevant to the pharmaceutical industry:

1. Humility about the limits of science is critical to enjoy the trust and respect of the public. Scientific analyses are not often trusted by the public. They often wonder at any given dose, why they should have to tolerate any risk.

2. Transparency is critical to maintaining the trust of the public as well as satisfying the expectations of trial attorneys. He predicted that the

[4]This section is based on the presentations of Dennis Paustenbach, ChemRisk; Jonathan Samet, Johns Hopkins University; Joshua Cohen, Tufts New England Medical Center; and Richard Hall, McCormick & Company, Inc.

[5]Sheila Jasanoff, Harvard University.

pharmaceutical industry will see an avalanche of suits in the future, as the chemical industry has for the past 25 years. He observed that every single award of any magnitude that he has seen over the past 10 years (in chemical industry law suits) has involved lack of disclosure, not actual outcome. Transparency provides the means to reconstruct scientific analyses to determine where objective quantitative methods end and professional judgment begins, and it allows for a better understanding of the uncertainty in analyses and conclusions.

3. Use quantitative techniques to describe uncertainty in risk estimates. He noted that there are methods than can be used to do this.

4. Acknowledge that genetic polymorphisms exist and that most have not been characterized. Genetic polymorphisms are responsible for multiple dose-response curves for some chemicals. The same is true of drugs.

5. Unlike chemical risk assessment, where safe doses can be estimated with confidence (because exposures are usually quite low, on the order of 1 in 100,000 or less), pharmaceutical agents often involve relatively high doses, making it difficult to pinpoint human safety. Some pharmaceuticals carry risks as low as 1 in 10 or 1 in 20, again pointing to the importance of transparency.

6. Clearly describe the benefits of taking the drug and compare this with the possible risks. Most Americans are taking a more active role in their medical decisions than in the past, and they want to know the benefit–risk relationship of the drugs they are considering. The challenge is in communicating that information.

7. Discuss with patients the risks of *not* taking a drug. Both patients and trial lawyers need to know this as much as they need to know the risks of taking a drug.

8. Remind the public about its role and responsibilities in minimizing the disease process. Be clear about the risks and benefits of taking a drug with other pharmaceutical or recreational drugs and the roles of diet, exercise, and other factors in the "total approach" to dealing with illness. This kind of information not only contributes to the patient's complete understanding but also impacts litigation.

9. Strong, credible, science-based regulators that perform with integrity and diligence protect industry from public suspicion—and tort litigation—and play an important role in building trust relationships between the public and industry.

10. Don't try to hide risks. In recent years, Americans have insisted that they be informed of all possible risks to which they are exposed. If the risk is clearly discussed, rarely will the public become angry with a manufacturer.

In conclusion, Dr. Paustenbach stated that after 30 years, chemical risk assessors have learned that conducting good scientific analyses is not enough. One has to be transparent, direct, forthcoming, and willing to acknowledge uncertainties in medical or scientific understanding.

Need for a Framework

Dr. Samet reemphasized the long history of chemical risk assessment and how the Red Book provided a much-needed formal framework for addressing environmental health risk questions. He discussed what is widely considered one of the best human data-based quantitative chemical risk assessments conducted thus far: radon exposure. He described the history of the EPA's awareness of the problem and the subsequent risk assessment process conducted by a National Research Council committee, of which Dr. Samet was the chair (National Research Council 1999).

He described how models derived from a quantitative risk assessment can be used to answer questions about risk at both the population level (e.g., what is the population risk?) and the individual level (e.g., if I have been living in a home with radon levels 10 times above the EPA's action guidelines, has my family sustained increased risk?). He noted that one of the key challenges of risk assessment is the reality that there are often multiple dose-response curves. He commented on the importance of using pooled epidemiological data and mechanistic knowledge to guide more certain risk models. His committee was able to derive a reasonably precise description of how risk varies with exposure because it had 100 years of epidemiological data on the relationship between exposure and cancer risk *and* a good mechanistic understanding of how radon might damage a cell and cause cancer. He also noted that uncertainties can be characterized and that understanding how uncertainty estimates change the behavior of decision makers is a relevant topic that has not received much attention.

Dr. Samet emphasized that pharmaceutical risk assessment needs a framework—its own Red Book—so that questions about risk and benefit can be asked and answered as precisely as possible. A framework provides a common understanding of concepts and terminology and serves as a foundation for readily identifying what information is needed in any given situation to accurately assess benefit–risk.

Lessons Learned from Pesticide and Mercury Risk Assessments

Dr. Cohen agreed with Dr. Samet that having a framework is critical. He noted that unlike the EPA framework, which is focused on reducing risk to acceptable levels and for the most part does not really con-

sider benefit (except when considering economic cost), pharmaceutical benefit–risk assessment (and management) demands a more comprehensive framework based on the recognition that risks do not occur in a vacuum and must be weighed with benefits.

Dr. Cohen's talk revolved around two case studies, the first involving a pesticide ban (Gray and Hammitt 2000) and the second mercury in fish (Cohen et al. 2005). He used both to demonstrate difficulties encountered when conducting benefit–risk trade-off analyses. He used the second study to elaborate on how some of those difficulties can be overcome. Specifically, Dr. Cohen and his colleagues used an alternative, QALY-based risk-assessment approach to evaluate the benefit–risk trade-offs associated with shifts in fish consumption. Their more comprehensive analysis and presentation of the data provided the public (and the professional community) with more meaningful information than a single reference data point.

Dr. Cohen concluded by noting that it is important to compare pharmaceuticals to realistic alternatives, not just to nothing (that is, placebos). While comparing to a placebo is a good starting point, accurate risk assessment ultimately requires a realistic comparison. He noted that outcome probabilities need to be quantified, particularly if they vary among individuals, which is the case with pharmaceuticals (e.g., people have different underlying risk factors and take different doses of medication) and that outcome severity needs to be quantified using clinical outcomes, not intermediary measures such as enzyme biomarkers. Finally, both the "natural unit" and common metric estimates should be reported. While these demands complicate pharmaceutical drug efficacy assessments and increase uncertainty, he said that there are ways to deal with the uncertainty.

Parallels Between Food and Drugs

Dr. Hall remarked that even though the U.S. Congress has combined foods with drugs in the same legislative act for the past 100 years, the differences between the regulation of foods and drugs are much more apparent than the similarities. He discussed the limited regulatory authority of the FDA and the greater complexity and uncertainty of measuring food-related risks (compared to measuring drug-related risks). He noted that, in contrast to drugs (with the exception of Olestra), there have been no clinical studies for safety or observation of possible adverse effects, and postmarket surveillance is uncommon (exceptions include aspartame and sterol and stanol esters in bread spreads).

Dr. Hall noted that while public perception of acceptable risk in food is zero, the unacceptability of risk is perception only. Obviously we do

accept risks, and food-borne illness is second only to the common cold as a cause of lost time from work, and obesity—a nutritional food-related risk—is widespread. The discrepancy between zero-risk perception and the acceptance of food risks exists, Dr. Hall argued, because the latter are regarded as voluntary. For example, weight gain is something that is within our control, so we don't think of it as a risk.

Dr. Hall concluded by remarking that dietary supplements reflect a trend toward the "medicalization" of food. If that trend continues, then perhaps the regulatory challenges associated with food will become somewhat more similar to those of drugs. For now, however, the risks and benefits of foods and the public perception of them do not offer many parallels to drugs.

This session ended with a brief discussion of risk communication and whether the discrepancy between public perception of risk and actual risk, in any of these situations, may stem from the fact that the public seems to be hearing exaggerated claims, not nuanced messages, about risks and benefits. Dr. Cohen remarked that yes, risk communication must be improved. In the case of mercury in fish, he argued that the FDA and EPA have worked very hard on improving their risk communication but that it still poses a problem. Regulators need to anticipate how people are really going to react to something and realize that they are not going to follow the recommendations exactly as advised.

Dr. Paustenbach emphasized the importance of clearly expressing what we have learned from quantitative risk analysis, including uncertainty analysis. He suggested that communicators conduct dry runs by communicating such information to stakeholders, for example in an afternoon session, and then immediately testing the communications package by asking the stakeholders what they heard. Dr. Hall agreed that conducting a communications dry run provides important information about what the listeners bring with them in terms of preconceived perceptions.

The discussion ended with a question about whether there are any circumstances in which it does not matter if information about risk is available. Dr. Paustenbach argued that from a legal perspective, there is no exception to complete transparency, disclosure, and communication of all information.

CRISIS IN CREDIBILITY[6]

A recurring topic of discussion over the course of the two-day workshop was loss of public trust in the U.S. drug safety system and wide-

[6]This section is based on the presentations of Brian Strom, University of Pennsylvania; David Slavin, Pfizer Inc.; and Lynn Goldman, Johns Hopkins University.

spread misunderstanding about the meaning of drug safety and the scientific process that moves drug approvals forward. Highlights are summarized here.

Dr. Strom identified three major sets of limitations associated with analyzing benefit–risk ratios early in the drug's regulatory life cycle. The first limitation is the experiential difference between premarketing and postmarketing drug use and the fact that *efficacy*, a measure of how well a drug works in an experimental setting, is very different from *effectiveness*, which is how well an intervention works in the real world. Second is the growing cost of drug development, which has led to an increased need for immediate blockbuster sales and aggressive marketing even though knowledge of adverse events is inherently incomplete prior to marketing. Third, premarketing studies are of short duration, which means that only the short-term effects are known at the time of marketing.

Dr. Strom commented on other limitations of the current system, including lack of incentives (e.g., to complete promised postmarketing surveillance studies) and the "historic" lack of commercial and regulatory interest in adverse drug events, both of which feed into public misunderstanding that drugs have zero risks at launch. He stated that direct-to-consumer advertising exacerbates the situation, leading to overuse of drugs by patients for whom use of the drug is not compelling and for whom there may be substantial risk of unknown adverse reactions.

The effect of these limitations is that the public misunderstands drug safety, believing that postmarketing discovery of adverse drug reactions means that "somebody messed up." In reality, almost all postmarketing safety issues involve rare adverse events that could not have been detected prior to marketing. This misunderstanding, coupled with growing concern about drug safety has led to overreaction, increased premarketing requirements, and delayed access to new drugs.

Dr. Slavin discussed how the regulation of science and technology has evolved from a culture of policy makers, industrialists, and scientists meeting behind closed doors, with citizen and stakeholder groups rarely consulted, to one where science is "just another stakeholder." The public now questions scientific results, including results about drug benefit and risk. Dr. Slavin remarked that high public trust is typically associated with low perceived risk and, conversely, low public trust with high perceived risk and eventually evidence resistance. He argued that the precautionary principle and growth of risk aversion have led to widespread expectation that there is always a new scandal around the corner and that it is "better to be safe than sorry." He disagreed with this public expectation.

Dr. Goldman discussed the results of a survey recently published in the *Wall Street Journal* (2006), demonstrating that while over time most people have thought highly of the FDA, the trend now shows

the public becoming increasingly dissatisfied. She argued that the biomedical research enterprise is driven increasingly by money; researchers are funded through consulting agreements with pharmaceutical companies and the medical profession is becoming less independent of the regulatory process. Those who used to be the trusted representatives of consumers (e.g., medical professionals, biomedical researchers) are no longer trusted by the public. She noted that there are few sources of funding for pharmacology research through the National Institutes of Health (NIH), FDA, or other federal sources, and funding is not allotted for independent data assessments, consumer surveys, or efforts to communicate with consumers about pharmaceutical risks. Dr. Goldman suggested that consumers be made equal partners in the process.

Dr. Goldman's presentation raised questions about whether there is any way to "turn the system around." The biomedical research enterprise is at a point where the best experts consult with industry and government on the same products. Dr. Goldman replied that the FDA has not created space for a consumer role in its culture and that the agency needs to encourage more dialogue among academia, industry, and especially consumer groups. Opening communication, she argued, will create a culture of collaboration and trust.

There were several comments on how the system needs to make room for relevant industry players to collaborate with the best scientific talent in order to bring good products to market. One attendee argued that by preventing an academic researcher who collaborates with industry on product development from participating in the regulatory process, one eliminates from the process those people who truly understand the intricacies and subtleties of the research and know enough to ask the right questions on behalf of patients. Another participant remarked that there are well-designed mechanisms in place at various agencies for disclosing acceptable conflict and identifying unacceptable conflict. While this is a complex issue, it can be addressed with integrity and balance.

Dr. Goldman suggested that the FDA open the door to dialogue to consumers. She relayed an experience that she had as a consumer testifying before an FDA advisory committee. She was struck by the absence of consumer input at that meeting. Consumers attending the meeting were extraordinarily disadvantaged by not having materials made available to them until immediately prior to the meeting. Making those materials available earlier during the process is an example of a small change that the FDA can make that would begin to make the agency more consumer-friendly.

Ms. Musa Mayer[7] commented that the FDA very judiciously and responsibly solicits comments from patients who serve as patient rep-

[7]Musa Mayer, patient advocate and Drug Forum member.

resentatives or consultants in various programs. When not serving in that capacity, however, she shares the frustration of other members of the public with respect to not being able to access materials until about 24 hours before the meeting and having such a limited amount of time for preparing comments.

Dr. Goldman further suggested that there be more public funding for pharmaceutical research, so that researchers have more options in addition to working with industry. This prompted some discussion about where the funding would come from, given that within academia there is no other clear path of advancement for pharmacological researchers. (NIH funding is the main path, but pharmacological researchers generally do not pursue it.) One participant remarked that there is really no such thing as an independent source of funding and that the challenge is to create diversity in funding sources.

Dr. Leiden argued that it is precisely these complex interactions between academicians, industry and to some extent regulators that are the reason for the success of the biomedical enterprise in the United States. If we are not careful in how we handle conflict of interest, in our attempts to untangle it, we may severely damage the system. He stated that the best evidence for this is that it wasn't until the Bayh–Dole Act of 1980 stimulated the translation of basic scientific discoveries in academia to applications in industry that the U.S. biotechnology industry emerged. Dr. Leiden mentioned a recent article reporting that there has not been a single case of research fraud caused by these financial conflicts of interest between industry and academia (Stossel 2005).

3

The Challenge of Communication[1]

The workshop next focused on the challenges involved with effectively communicating risk information, Dr. Lipkus presented an overview of the issues.[2] Clinical barriers (for example, limited patient involvement in discussions, limited time) make it difficult for physicians to effectively communicate about risks and benefits with their patients. Physicians tend to underestimate the amount of information that patients want, control discussions and discourage patient involvement, overestimate how much patients know, overestimate the efficacy with which they accomplish important communication tasks (how well they have communicated information to their patients), and have limited time.

Furthermore, physicians and patients understand risk differently. He referenced a study in which patients identified "possible side effects" as the most important piece of information to consider when making a decision about a drug (Berry et al. 1997). Physicians, however, ranked side effects tenth among 15 items, and the number one consideration for physicians was "interaction with other drugs for long-term use."

While most physicians agree that conveying risk in a quantitative format is important, very few are confident in their ability to do so. In

[1]This section is based on the presentations of Isaac Lipkus, Duke University; Steven Woloshin, Dartmouth University; Lisa Schwartz, Dartmouth University; and Lynn Goldman, Johns Hopkins University.

[2]For a heuristic framework to aid in understanding risk, Dr. Lipkus referred workshop participants to Weinstein 1999.

a study of primary care physicians in Massachusetts, 93 percent agreed that conveying risk numerically is important, and 63 percent felt that quantitative and qualitative communications are equally important, but only 36 percent felt that they could convey numerical risk information effectively (Gramling et al. 2004). One of the most difficult challenges in risk communication is conveying probabilistic information. The difficulty stems in part from the fact that most patients are interested in what their own chances of benefit and risk are, not population-level probabilities.

If physicians are not confident in their ability to communicate risks numerically, what can be done to help them? More generally, how can risk information about medication be communicated effectively? The magnitude of this challenge is evidenced by the fact that even after several decades of effort and a large body of evidence, there is still a lack of consensus concerning the most appropriate method by which to communicate medical risk.

Both individual-level (information directed toward the individual patient) and population-level (information about the population of which the individual is a member) risk information can be communicated in any of several formats—numerically, verbally, visually, or through the use of narrative. Numerical formats for presenting risk include percentages (e.g., 10 percent greater risk), frequencies (e.g., 1 out of 10 people is expected to have side effects), classical probabilities (e.g., 0.10 chance), and "numbers needed to treat" (e.g., need to treat 100 people to get one person to benefit). The advantages to using numbers include the following: they are precise, they add an aura of "scientific credibility," they are easy to compare and convert to varying metrics, they can be used in existing or new algorithms, and they are verifiable. Numerical usage also has disadvantages, such as the discrepancy between actual (or objective) and perceived risks that results when numerical risk information is used, even just moments after the information has been provided. Dr. Lipkus stated that studies have shown that innumeracy is problematic across all educational levels, even among the college educated.

The problem of innumeracy raises the question, Why can't we just verbally communicate the risk? Verbal terms tap into gut-level reactions, they seem to be easy, and they convey uncertainty on multiple levels. Yet verbal communication is vague, terminology is difficult to standardize across contexts and between people, and interpretation is highly variable.

If not verbal, how about visual communication? Visual aids can range from bar charts and line graphs to risk ladders and stick figures. The advantages of visual displays are that they can summarize lots of data; help the patient see patterns that would otherwise go undetected; help the patient perform some mathematical operations, such as comparisons,

automatically; and attract and hold the patient's attention because the data are displayed in concrete, visual terms. However visual aids have their drawbacks too: data patterns may discourage people from paying attention to details; some visuals, such as risk ladders, are poorly understood unless they are explained; creating visuals usually requires technical programming; and we don't really know how visual aids affect risk perception.

Dr. Lipkus concluded his talk by posing a final challenge: What should the outcomes of risk communication be? He argued that we spend a great deal of time discussing how to communicate risk, but we don't spend much time discussing what the outcomes should be. For example, does risk communication lead to higher or lower rates of adherence? Does risk communication lead to more or less conflict or mistrust? Does it unnecessarily increase anxiety or other negative emotions?

PRESCRIPTION DRUG FACTS BOX

The 1938 Food, Drug and Cosmetics Act, the basic law that established the FDA's actions, reads: "Information in drug labels should appear only in such medical terms as are not likely to be understood by the ordinary individual." Although the law has been amended since then, Dr. Woloshin argued that sometimes it still feels as though we are still trying to live by its spirit, particularly when it comes to direct-to-consumer advertisement.

Dr. Woloshin showed a series of direct-to-consumer drug advertisements, demonstrating their lack of accurate factual information. Some ads assert efficacy rather than provide data (e.g., "works for me"); others contain data about popularity but, again, nothing about efficacy (e.g., "more than one million people have begun using Rezulin to help manage diabetes"); some contain data irrelevant to the assertions made; and still others contain incomplete information (e.g., informing that the drug cuts a risk "by nearly half," raising the question, half of what?).

Dr. Woloshin commented on the brief summaries of harm information that the FDA requires to be included in all advertisements. He remarked that while the FDA has recently issued new guidance to industry about providing these summaries in a user-friendly format, the fundamental problem about the lack of efficacy data remains. If consumers are going to make benefit–risk decisions, they need to have access to both benefit and risk data. Only if they know what the benefit is, will they be able to make informed decisions about whether the risks are worth that benefit.

Dr. Woloshin discussed a possible solution for providing user-friendly benefit–risk data in advertisements: the Prescription Drug Facts Box. Modeled after the FDA's Nutrition Facts Box, this box would contain the data from the brief summary but in a simple tabular format. He showed a

prototype of the Prescription Drug Facts Box with two parts: the first part containing descriptive information (answering questions such as, What is the drug for?), the second part containing a data table including both risk and benefit information (likelihood of intended outcome if the drug is taken versus not taken; likelihood of risk if the drug is taken versus not taken).

Dr. Woloshin described two studies that he and his colleagues conducted in an effort to determine whether the Prescription Drug Facts Box is effective—that is, if it helps people understand and judge the benefits and harms of drugs. In one study, researchers concluded that not only were the boxes easy to read and were preferred by participants (compared to ads without the boxes), they also helped participants more accurately interpret the drug's benefits (Woloshin et al. 2004). In the other study, researchers found that participants across a range of educational backgrounds did quite well in interpreting extracting, manipulating, and applying both benefit and risk data.

Questions were raised about the discrepancy between Dr. Woloshin's encouraging results with respect to patients' abilities to analyze, digest, and make fairly sophisticated decisions about benefit–risk information and Dr. Lipkus' less optimistic perspective. Dr. Woloshin responded that the explanation probably is in how the information is provided. He and his colleagues chose methods and representations, including a simple tabular format, that had been shown to be understandable and accessible even to less well-educated people. He said that the boxes have been through countless iterations and were based on large numbers of focus groups and cognitive interviews. Dr. Lipkus agreed that the tabular format made it easy for people to find the information they need. He also noted that presenting numbers in two ways, as the box does, could provide multiple senses of meaning. He remarked that some of the studies that he reported utilized more complex information.

Dr. Fendrick remarked that his work has shown that informed patients become more anxious and less likely to undergo screening and that many patients want their physicians to make the decisions. He also expressed concern about whether efficacy data drawn from registration trials is suitable for labeling, given differences between efficacy and effectiveness.

PHYSICIAN USE OF THE PRESCRIPTION DRUG FACTS BOX

Dr. Schwartz argued that the Prescription Drug Facts Box would also help physicians make better prescribing decisions by providing a fast, efficient way to access information. She remarked on the limitations of several ways that physicians currently access drug information:

1. Information provided by drug company representatives is often selective and incomplete.

2. Many clinical trials are not published, many are not published in journals that physicians regularly read, and not all peer-reviewed journal articles report all the benefits and risk measured during a clinical trial.

3. Brief summaries that accompany advertisements in medical journals, newspapers, and magazines typically do not include efficacy data; when they do, the data tend to be incomplete or exaggerated.

4. FDA approval labels, or package inserts, have much more complete information than these other sources, but there is some question as to how often clinicians read those inserts.

5. FDA drug approval documents, including medical, chemical, statistical, and other reviews of drug company applications, are freely available on the Internet;[3] however the large quantity of critical data, lack of structure, and difficult reading make accessing the information overwhelming.

In addition to improving physician decision making, Dr. Schwartz argued that the process of creating a structured table of rates of outcomes for all the treatment groups can reveal whether and which patient outcomes are unavailable or missing from the label. She used a prototype Prescription Drug Facts Box for Zometa to illustrate. By sifting through the drug approval documents, she and colleagues discovered a statistically significant dose-related difference in mortality that had been noted but without any strong warning bells. Nor was the difference included in the current label. Dr. Schwartz argued that the mortality finding warrants a stronger statement.

Dr. Schwartz remarked that one of the challenges of presenting side effect information is doing it so that people can sort through the multiplicity of side effects, which requires establishing arbitrary rules for deciding which side effects to include. Her team decided, for Zometa, to make separate rules for life-threatening and symptom side effects. Specifically, life-threatening side effects would be included if the *p*-value was 0.5 or less with respect to the difference between the drug and the comparison. A large *p*-value was chosen to prevent missing potentially life-threatening harms. Symptomatic side effects, by contrast, would be included only if the *p*-value was less than 0.2, limiting unnecessary concerns. There were concerns, however, that manipulating statistical precision in this manner could ultimately harm the integrity of the process.

Dr. Galson remarked that FDA drug labels are in fact undergoing total transformation; that there is going to be a standardized format, which the

[3]See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

FDA has been working on for some 10 years; and that changing the format of the labels is in practice very difficult. Additionally, the FDA is working with the National Library of Medicine to move all labels onto the latter's website, in a machine-readable format, giving people the opportunity to examine the data (through hyperlinks to full prescribing information) and make their own facts boxes. He opined that while these changes are certainly expected to improve communication, we still have a long way to go. For example, various types of graphics might be better than words in explaining the different components of benefit–risk ratios.[4]

LESSONS LEARNED FROM THE EPA

Dr. Goldman noted that there were two types of safety communication: routine and crisis. She relayed lessons learned about both from her experience with the Environmental Protection Agency.

She described how the EPA's Pesticide Consumer Labeling Initiative[5] found that while the language on labels seemed to be complete, it was often unintelligible and useless. In response, the EPA changed its standard labeling language; conducted more comprehensive research to find out in more detail what kind of information people wanted and how they could best find that information; took a top-down approach to reforming the internal process of managing and developing labels; and ran a campaign to encourage consumers to read labels.

Dr. Goldman showed the label from a prescription drug and remarked on two features of the "Information for Patient" section. First, she noted the difference between information and facts, arguing that the labels included only the latter and that not even her physician could understand them. Second, she observed that there is no indication of what judgment the FDA made about the risks of this drug. She argued that the label demands too much of patients—not only must they find a way to understand these facts, but they also have to make their own judgment about what the risks may be. She asked why we are afraid to tell consumers what the FDA's judgment is, in plain language.

She described a 1994 crisis situation, when an FDA market basket survey detected an illegal pesticide, chloropyrifos-ethyl, in oat cereal and discussed how the EPA and FDA cooperated on risk assessment and communication strategies and successfully resolved the situation.

Dr. Goldman suggested that we study the information needs and preferences of consumers and learn how to communicate in their language, and that we develop procedures for making decisions quickly and

[4]See, for example, Edwards et al. 2002.

[5]See http://www.epa.gov/opptintr/labeling/index.htm.

collaboratively in crisis situations and then informing the public about those decisions.

Dr. Goldman's suggestion that more judgment be put in the materials that the FDA gives to consumers prompted a comment that this was very different from Mr. Hutt's argument (see Section 4) that patients be given the facts only and be allowed to make their own judgments. It was noted that this is an excellent demonstration of the fact that very reasonable people have diametrically opposed views about what the FDA should do on any given matter.

A comment was made about how much of the workshop discussion focused on academics, industry and consumers, but that the entire FDA regulation process relies on the prescribing physician as a critical "learned intermediary." The complete absence of participation by such groups in the FDA regulatory process is striking. While, in the past, efforts have been made to build relationships with medical professional organizations, budgetary constraints have eliminated that component from the agency. Little has been done to reestablish those relationships and have had varying degrees of success in trying to partner with them. Dr. Goldman noted that this is why she mentioned how difficult it is for physicians to understand some drug labels. She agreed that they are "out of the loop." Dr. Leiden agreed and noted that "opinion leaders" practice in highly controlled academic medical centers where drugs are used very differently than they are in the "real world." We need to consider the knowledge and input of practitioners who are regularly seeing patients and prescribing drugs.

4

The Importance of Context in Healthcare Decision Making[1]

An overarching theme of the workshop discussion was that the ultimate goal of improving benefit–risk assessment and communication is to enable "better" healthcare decision making. Dr. Fendrick observed that there are two outcomes of better decisions: (1) reducing patient risk by decreasing the use of drugs that people want to take but wouldn't take if they were better informed; and (2) enhancing benefit by increasing the use of drugs that people don't want to take now but would if they were well informed. Participants identified and debated major constraints of the current system that hinders patients (and physicians) from making optimal decisions.

ON-THE-SPOT DECISION MAKING

Dr. Slovic argued that understanding the psychology of judgment and decision making is critical to effectively designing, presenting, and utilizing pharmaceutical benefit–risk information. In order to determine how people perceive and assess benefit–risk relationships, he listed some assertions that we need to consider: there are different types of decisions about benefit and risk of pharmaceuticals; risk is not a well-defined concept, and cavalier use of the word may contribute to the challenges associ-

[1]This section is based on the presentations of Paul Slovic, Decision Research; Peter Ubel, University of Michigan; Sheila Jasanoff, Harvard University; Hal Sox, *Annals of Internal Medicine*; Carl Spetzler, Strategic Decisions Group; Kevin Schulman, Duke University; and Peter Barton Hutt, Covington & Burling LLP.

ated with communicating benefit and risk information; when faced with a benefit–risk decision, people tend to behave more intuitively, by sensing the qualities of whatever it is we are deciding and then integrating those qualities very quickly and automatically; patient perception of benefit and risk is just one of many factors at play when a decision is made about drug usage; when forced to confront trade-offs, people become uncomfortable and may use a simple rule to determine the decision or avoid making the decision altogether; and lastly, people must acquire and comprehend benefit–risk information before they can process it.

Dr. Slovic raised the question, Assuming that a patient acquires and comprehends this information, how does he or she make decisions involving benefit and risk? He argued that rarely do ordinary individuals explicitly calculate benefit–risk trade-offs when making a decision. Patients make on-the-spot, experiential decisions that are influenced by a complicated set of interacting factors, such as physician decision (the physician is making the decision about what is best), patient perception of benefit and risk (e.g., associating high benefit with low or zero risk), and innumeracy. Patients rely on their own knowledge, feelings, and memories when constructing preferences, and the way that information is presented or framed can readily alter their decisions. There are no neutral frames, so this poses a tremendous challenge to communicating benefit–risk information. Every presentation of information creates a bias one way or another, and whoever frames the decision inevitably manipulates the choice.

Dr. Slovic discussed affect, one of the many powerful elements of preference construction. He defined affect as a valenced feeling (e.g., goodness or badness) associated with a stimulus. It involves the processing of feelings associated with stimuli in what is known as the "experiential mode" of thinking, in contrast to the "analytic mode."[2] These two types of thinking—experiential and analytic—reside side-by-side in our brains and play off each other in "the dance of affect and reason." Researchers are currently trying to understand how these two ways of thinking interact and have demonstrated thus far that experiential decision making increases with innumeracy, cognitive load (e.g., the complexity of the task and information), stress (e.g., time pressure), age, and the accompaniment of affect-rich images with the information. Studies have also demonstrated that although, in reality, risk and benefit are generally positively correlated, in people's minds they tend to be strongly negatively correlated. This is because people judge benefits and risks based on feelings, with beneficial activities typically associated with lower risk.[3]

[2]See Epstein S. 1994. Integration of the cognitive and the psychodynamic unconscious. *American Psychologist* 49:709–724.

[3]See Alhakami AS, Slovic P. 1994. A psychological study of the inverse relationship between perceived risk and perceived benefit. *Risk Analysis* 14:1085–1096.

Innumeracy is another major factor in preference construction—it has been associated with lower comprehension, greater framing effects in decision making, a greater influence of affect and emotion on decision making, and drawing less meaning from numbers.[4] Innumeracy raises the question, How should a clinician convey risk information to a patient—as a relative frequency, percentage, or otherwise? Dr. Slovic suggested that the answer depends on how the communicator wants to bias the patient, for example, whether he or she wants the patient to become worried or remain calm.

Context Matters

Dr. Ubel corroborated Dr. Slovic's thesis: a range of contextual factors affect people's perceptions of risk versus benefit and guide decision making. Dr. Ubel posed several hypothetical benefit–risk choices to the audience and described what he and his colleagues have learned from posing similar choices in controlled studies. Their findings reflect the reality that benefit–risk decision making depends on subtle contextual factors:

- *Feelings* (or, as Dr. Slovic called it, "affect"): People do not always make rational use of information about their preferences or the risk(s) at hand. Rather, the way people *feel* about a decision or risk(s) guides their decision making.
- *Guessing*: If somebody has already guessed or imagined what the risk of something is before knowing what the actual risk is, he or she will feel differently about the risk (e.g., anxious versus relieved) and make a different decision accordingly.
- *Type of information provided*: Patients' perceptions of risk and the decision they make depend on what they are told about average risks for the population at large and how that determines whether they perceive their risk as high or low.
- *Emotional salience of possible outcomes*: Many possible outcomes have emotional salience, which affects how people think about risks and how they use probability information (or don't use it) in their decision making. (For example, colostomies and diarrhea are "icky" things that elicit emotions and affect people's decision making about treatment options.)
- *Labels and words*: Some words and terms scare people (e.g., "mad cow disease"), whereas others do not (e.g., "bovine spongiform encephalopathy"), influencing decision making.

[4]See, for example, Peters E, Vastfjall D, Slovik P, Mertz CK, Mazzocco K, Dickert S. 2006. Numeracy and decision making. *Psychological Science* 17:407–413.

- *Where the risk is located*: People make different decisions when the risk is "external" (e.g., risks associated with vaccines) than when the risk is "internal" (e.g., a tumor).
- *Betrayal aversion*: People make different decisions if they have felt betrayed in the past by something that should have protected them.
- *Knowledge about the risk*: As uncertainty about the risk of doing something—or not doing something—increases, the influence of contextual factors increases. If nobody can pin down the probabilities, then all of these other factors are going to drive the decision making even more.

Dr. Ubel pointed to the need for improved risk communication. The fact that context is so important raises the question, How can benefit–risk decision making be improved?

Reframing the Context

Dr. Jasanoff stated that arguing context matters, as Drs. Slovic and Ubel have done, is only the beginning of a discussion. The next question is, *What* context? She emphasized the importance of understanding where responsibility for benefit–risk decisions lies. While our legal system gives informed, competent patients the ultimate decision-making power with regard to which therapy to choose, there are also some legally regulated associative responsibilities that lie elsewhere. For example, companies are responsible for producing beneficial products, regulatory agencies for enforcing a certain level of safety, and physicians for implementing the standards.

Dr. Jasanoff discussed how several decades of social science research on risk have led to the finding that many regulators and other people with associative responsibilities for benefit–risk decisions operate under the rules of what is known as the "deficit model of the public." This model is based on several assumptions: (1) Public risk perceptions are influenced by systematic cognitive biases, (2) These cognitive biases produce erroneous assessments of probability, and (3) These erroneous assessments of probability lead to incorrect weightings of relative risks and benefits, which need correction through appropriate expert advice.

By contrast, the legal system presupposes something that does not resemble this deficit model at all. U.S. law operates on the assumption that the public is a constantly learning, evolving entity composed of citizens who are knowledgeable, informed, and capable of absorbing evidence. Based on this notion of the knowledgeable citizen, the rights of the public include the right to know, a patient's right to give informed consent, the right to demand reasons of our agencies, the right to participate and offer expertise, the right to challenge irrational decision making,

and the right to appeal judicial rulings. This "public-under-law" model is extraordinarily important to the functioning of a democratic society. Under this model, we assume that lay people are capable of understanding and critically evaluating complex technical information. They must continually be learning in order to assert the rights of citizenship in our modern knowledge-based society. We also believe that lay people have nonbiased perspectives, knowledge, and insights that are essential for good decision making and that ought to be incorporated into decision-making processes.

Dr. Jasanoff described two different ways to imagine the public's involvement in benefit–risk decision making. First is the "education model," in which somebody knows best or better, and somebody else needs to be brought up to speed. Under the guise of this model, the choices are to some extent framed in advance, with the expert controlling the style of communication and the objective being to get the most rational outcome—rationality being defined in relation to quantitative outcome measures. Second is the "engagement model," under which public involvement is based on the notion that citizens are continually learning. Under this framework, choices are not framed in advance, rather they are framed through dialogue. The way that the information is conveyed is targeted toward evolving questions and is not controlled by the expert. For example, in situations where patients are paralyzed by too much benefit–risk information, if the right kind of dialogic environment were selected, then perhaps counseling could help the patient get past this paralysis. The objective is not to get the most rational outcome from the perspective of an agency (e.g., in terms of how much money is appropriate to spend) but to get the most beneficial outcome for the patient.

Dr. Jasanoff proposed that the following contextual factors be considered when thinking about how to improve benefit–risk decision making: view the public as partners, not antagonists, at all levels (regulatory, physician–patient interaction); express uncertainty and ignorance; diversify communication strategies; adopt an experimental approach to approval, communication, and learning (rather than a marketing approach), including a postapproval means of providing feedback and implementing corrections; and improve our sense of responsibility, given that we do not live in a zero-risk world and that people will inevitably get hurt.

Engaging the Patient

The notion of engaging patients in the decision-making process, as Dr. Jasanoff discussed, raised a question about how this could be done. Specifically, who should frame the information, and how should that

information be communicated to the public? Under what circumstances and to what extent should physicians have detailed quantitative discussions with their patients about the risks and benefits of a drug or procedure? Dr. Slovic said that it is a hard question to answer because there are so many different types of publics and patients. Some patients don't want that information, others wouldn't know how to use it, and still others want to know everything. Dr. Jasanoff emphasized the lack of time as a limiting factor in our decision making and how many patients may not have time to consult with their families. She said that many patients may not be given the opportunity to indicate in what context they would like to receive benefit–risk information, for example hearing it verbally versus seeing it visually. Dr. Ubel reflected on how difficult it is to explain risks and benefits in clinical settings, particularly when office visits are so short. Physicians need to be aware of innumeracy and other factors that influence patient perception of risk. The medical curriculum needs to be improved to help doctors become better communicators.

Dr. Leiden concluded the session by observing that despite the complexities and difficulties of benefit–risk decision making, there is a need to provide the public with much better education of risk and benefit concepts so that patients become more involved with the decision-making process regardless of how the information is presented.

RATIONAL DECISION MAKING AND UTILITY ASSESSMENT

Dr. Sox stressed the importance of helping patients make rational decisions. He introduced a model for rational choice known as "expected value decision making" and used a Las Vegas slot-machine metaphor to explain the model. While a gambler's winnings are unpredictable, given that he or she is playing a game of chance only a few times, the owners of the slot machines are in a different position. Given that their machine is played tens of thousands of times a year, their winnings are predictable. Dr. Sox likened the experience to that of a patient with a given illness. While the patient's outcome is unpredictable, given that he or she is experiencing an unpredictable situation only once, the physician will pick the treatment that has worked in the largest number of patients over the course of his or her career. While they cannot guarantee an outcome, physicians maximize patients' chances of having the best possible outcomes by choosing decision options with the highest expected values. Like the slot machine owner, the physician is an expected value decision maker.

Dr. Sox then explained how a "decision tree" is used to make rational decisions based on the expected value decision-making model. He described two ways to present the outcomes—a tree format and a balance-

sheet tabular format. The problem with both of these methodologies, however, is that they express outcomes in terms of life expectancies, and a year of health (e.g., after being cured) is given the same value as a year of illness. Based on the premise that sick years are not worth as much as healthy years, however, outcome states should have different values. To account for the difference in quality of life, life expectancy must be multiplied by utility to yield QALYs. Utility is a measure of preference that takes into account how the patient feels about the outcome state. Either average utilities (average among all patients) or personal utilities (an individual's personal preferences) can be used to calculate QALYs.

Dr. Sox demonstrated how utilities are used to measure QALYs, using data from a 1995 study (Nease et al. 1995). He discussed different methods for estimating utility, including the "standard reference gamble," the "time trade-off method," and the use of a linear scale. He concluded by discussing the challenges of measuring utility and emphasizing that despite these challenges, quantifying attitudes toward health states (measuring utility) is doable.

Patient-Centered Approach to Decision Making

Dr. Spetzler elaborated on the principles that underlie benefit–risk decision making:

- The system should be patient-centered and should empower the patient.
- Instantaneous consumer responses gathered in an experiment are not necessarily the same decisions that would be made by that consumer as a patient. Most treatment decisions include family members and other trusted advisers.
- Decision making is not equal across individuals. While some people learn the basics of good decision making through experience, others do not.
- Treatment information should be decision-friendly—patients and their advisers should clearly understand the likely consequences of each alternative, and the preferences of the patient should be respected, even if they are judged unstable by their advisers.
- In a patient-centered approach, drug benefit–risk decision making is usually within the frame of a broader treatment decision that likely includes non-drug options. Every alternative needs to be considered, including "do nothing." While it may be impossible to include consideration of all of the alternatives in a package insert, one option might be to have some kind of independent information organization or rating agency provide comparative information.

Lastly, Dr. Spetzler suggested that if the system does not accomplish the above, then the system should be changed.

Dr. Spetzler argued that in order to make a good decision, a patient must be able to answer the following questions:

1. What is it that I am deciding, and why? If the frame changes, the decision changes.
2. What are my choices? Within that frame, there must be creative, doable alternatives.
3. What do I know? There must be meaningful, reliable information for each alternative. The Prescription Drug Facts Box provides information about one but not all alternatives. The information should be forward-looking since, although it is based on past experience, it is there to enable the decision maker to make predictions about the consequences of the decision.
4. What consequences do I care about? There must be clear values and preferences, or utilities.
5. Am I thinking straight about this? There must be logically correct reasoning—a way to sort through the alternatives, information, and personal preferences in a world of uncertainty and risk and derive a choice that gives the decision maker the most of what he or she wants. Ultimately, however, decisions are not purely rational; a good decision makes sense and feels right. People combine their heads and hearts, or the psychosocial and analytical, in decision making all the time. We have to know how to line those dimensions up—how to engage patients and go through the reasoning with them.
6. Will I act? There must be commitment to follow through. Much of this depends on whether a patient owns the decision.

Dr. Spetzler said that financial decision making is a good analogy for medical decision making. He noted that the financial industry has rating agencies, such as Dun and Bradstreet (D&B) and Standard and Poor's (S&P), and that the drug industry could do the same. He argued that there is no reason that the FDA should bear responsibility for this. In fact, distance from the regulatory agencies might make it easier to ensure that decisions are truly customer-focused. He concluded by arguing that the challenge is to bring this information to people who are not very numerate because we are not going to change the fact that most people are math-phobic.

How Patients Make Decisions About Therapy

Dr. Schulman presented three case studies representing typical treatment decision-making situations: a 70-year-old healthy female patient

who refuses flu vaccination because she thinks she will get sick from the vaccine; a 40-year-old male patient with new-onset malignancy who chooses experimental therapy with a high risk of toxicity; and a 60-year-old female patient with new-onset heart failure after a previous heart attack who is offered implantable cardiac defibrillator therapy as well as a new experimental heart failure medication. He then went on to describe how these three different people might consider their treatment options.

He noted that there is often a huge difference between a physician's review of the data and how a patient perceives the data, and that expectation about what is going to happen to a patient's life changes when his or her physician presents new information about the prognosis. He and his colleagues postulated that this type of change in one's position (receiving a new prognosis) can change the decision-making process and they constructed a model based on this. They called their model the "health stock risk adjustment model."

Dr. Schulman explained how, within a prospect theory framework, the model can be used to predict whether a patient is making a treatment decision under a condition of gains (risk aversion; more interest in avoiding risk than gaining benefit; not much toleration for uncertainty around risk) or losses (risk seeking; more interest in benefits than in risks; will tolerate uncertainty around benefits).

He explained how this approach can be used to predict treatment decisions of his three case study patients: (1) The 70-year-old woman is making a decision under a condition of gains and therefore is going to be incredibly conservative and focused on the toxicity issues. (2) The cancer patient is making a decision under a condition of losses, unless he has accommodated to his prognosis such that the presentation of new information doesn't change his perception of what life is going to be like. (3) The heart failure patient could be making a decision under either gains or losses, depending on whether she readjusted to her health state following the previous heart attack.

Dr. Schulman concluded by emphasizing that patient expectations and evaluations of risk and benefit vary across disease categories or indications. He suggested that while clinical trials are performed, research be conducted to determine how people make trade-offs between risks and benefits as well as how much uncertainty (in benefit and risk measurements) they will tolerate.

Limiting FDA Authority and Policy

Mr. Hutt argued that the FDA's authority should be limited to three main functions:

1. Assess potential harm, as it currently does.
2. Determine the probability that the drug may benefit one or more patients. The focus should be on the individual patient, not the population.
3. Require that all of this information be provided in detail in the best way possible (e.g., in a physician brochure, which might include more detailed scientific elements, and in a mandatory patient brochure).

By limiting the FDA's authority to these functions, a drug would be approved once a point is reached at which there are enough data to assess safety and risk and enough data to evaluate benefit or lack of benefit. The benefit–risk decision would be given back to the patient and the patient's physician, which is where the decision was originally placed under the 1906 Food and Drugs Act and 1938 Federal Food, Drug and Cosmetic Act.

Mr. Hutt provided a brief overview of the history of the FDA statute, noting that it wasn't until 1962 when the FDA became responsible for making benefit–risk decisions, even though the FDA's legal and congressional mandate to evaluate benefits and risks did not change. He argued that the transfer of benefit–risk judgment back to the individual patient would not change anything the FDA does with respect to analyzing either safety or effectiveness. Indeed, it would increase the amount of information made available to the American public and the people who need the information in order to make personal decisions. There would be full, complete disclosure to physicians and patients, with the FDA retaining power to prevent the marketing of outright poisons and to prohibit the marketing of drugs with no efficacy data or where there is no difference in outcome between the test drug and a placebo. Efficacy data would be presented to the public such that individual patients could decide whether they want to accept the risk in order to gain the possibility—not probability—of benefit.

Mr. Hutt discussed several reasons why this approach of limited FDA authority should be adopted. First, it respects the autonomy and humanity of every individual citizen. Paternalism is not a high value in our country, and the FDA has lost eight straight court cases because it has been accused of unnecessary paternalism. As Dr. Hall pointed out in his discussion of food risks, we each make our own decisions when we choose which foods to eat, given the information on nutrition made available. Drugs should be no different. Just because a patient doesn't follow advice doesn't mean that the patient is making a wrong decision. It may be the right choice for that patient. Second, when the FDA decides that it is not in the public interest to permit a drug to be marketed—taking the decision away from the individual—this can be a death warrant for that

individual. Third, it would encourage industry to pursue the development of products that may have unanticipated uses, which often become the most important uses of many products. With the current system, the development of drugs that demonstrate slight toxicity or that do not show great benefit early on are discontinued. Fourth, it would eliminate the current stranglehold of statistics over drug development. Patients don't care if the *p*-value is 0.05 or 0.5. While, yes, we need to let the consumer know what the odds are, if we calculate and present the information in a brochure, patients should be allowed to make their own choice. Finally, he asserted that a shift in paradigm would take the FDA out of the uncomfortable position it is currently in—of deciding who lives and who dies. That was never intended, and it is one of the contributing factors to the serious downgrading of FDA's credibility and trust in this country.

Paternalism Versus Libertarianism

Mr. Hutt's presentation elicited much debate. Dr. Strom remarked that he has dramatically less confidence than Mr. Hutt does in an altered, "libertarian" approach for several reasons. Dr. Strom said he has much less faith in the ability of physicians to understand the data. He remarked that he spends much of his time educating physicians to use safety data rationally. The problem stems partly from physicians not being aware of the data, partly from marketing pressure, and partly from physicians not knowing how to interpret the data. Additionally, Dr. Strom said he does not think that patients are able to balance the benefit and risk information correctly. In fact, this is why physicians go through the training that they do—to be able to make that kind of judgment. He pointed to Vioxx and said that the problem was poor prescribing. Most of the people who were prescribed the drug were not in the patient group for whom it was intended—patients who could not take NSAIDs (nonsteroidal anti-inflammatory drugs). If the patients taking Vioxx had taken NSAIDs instead, they would not have been exposed to the risk and Vioxx would not have been withdrawn. He argued that we cannot rely on the marketplace to make decisions about benefit and risk.

Mr. Hutt responded by arguing that, under his proposed changes, drug products would still need to go through an FDA approval process, which would include determination of risk and benefit. The only difference between the current system and his proposed system is in who makes the judgment as to whether a drug can or cannot be used. With regard to whether consumers and physicians can understand all of the benefit–risk information, he observed that the same argument was made with regard to nutrition labeling—that people will not understand the information and will eat the wrong foods for the wrong reasons. Yet if

you do not put the information on the label, Mr. Hutt argued, nobody will have a chance to understand the information. He referred to Dr. Jasanoff's argument about people having personal views about what is right and wrong and that our citizens are capable of understanding basic issues.

The discussion turned to statistics. Mr. Hutt argued that while the current system should retain its rigorous evaluation of safety and benefit, it must break out of its "statistical stranglehold." When statistics dominate the entire drug regulatory approval process, he argued, the end result is distorted because it does not account for individual variability. People that could benefit from a drug never benefit. He argued that if, instead of statistics, we could rely more on labeling, people would have greater free choice.

Dr. Strom responded that while he agrees about the concern for losing variability in the "tyranny of the mean," it is important to differentiate between throwing out all statistics and throwing out incorrectly done statistics. He cited pharmacogenomics as a good example of where there are a priori reasons why you would expect a subgroup to react differently and where analyses of means would give the wrong answer. With respect to labeling, he argued that studies have shown that current labeling does not change behavior. He said that other approaches may change behavior but we cannot assume that they work (as we assumed for so many decades that labels worked). The burden is on those who want to use an approach to prove that it works before pursuing it and expecting that physicians are going to prescribe correctly. Even in controlled settings, such as university hospitals, educational efforts to change prescribing behavior do not work. Until proven otherwise, the only way we can change prescribing is by changing availability of the drug.

Mr. Hutt asked whether a cancer drug with limited statistical efficacy (for example, a 0.2 *p*-value) would automatically be disapproved, even if there were no other drug available for that cancer. Dr. Strom replied that the drug should be available on a compassionate investigational new drug basis to select individuals, and that those individuals should be included in studies to determine whether the drug works or not. Mr. Hutt expressed concern that if the manufacturer were a small biotech company without the resources to provide the drug at no cost, patients who would otherwise benefit would be dying. Dr. Strom said that under those circumstances, society would decide to make the drug available through the National Cancer Institute, for example, or another organization. Mr. Hutt replied that, still, patients would need to wait, so that is not a good enough answer.

There was a comment that nobody had challenged Mr. Hutt in his assertion that we should approve drugs even if just one patient has the possibility of gaining benefit. The questioner argued that this means that

essentially every drug would be approved but without any reassurance of a reasonable expectation of benefit and that we would be exposing people to the burden of risk with potentially a false hope of efficacy. Trust in the process would erode, and companies could have greater liability in situations where they had not rigorously evaluated benefit. The question then becomes, "Who in society bears the cost?" Mr. Hutt responded by emphasizing, again, that approval would require separation in the clinical trial between the active agent and a placebo. Dr. Strom remarked that 50 percent of studies would be positive in that direction—showing benefit—when in fact the drug does nothing. Mr. Hutt said that the *p*-value ought to be in the labeling so that patients know the results of the clinical trial. With regard to false hope, Mr. Hutt reemphasized that his proposal is based on freedom of choice and the assumption that people are intelligent and capable of being educated.

Dr. Slavin remarked that the debate between Mr. Hutt and Dr. Strom misses the point. Rather than dissipating our energies in deciding who is going to make decisions about whether drugs can be used or not, there are more immediate issues such as risk communication and trust that can and should be addressed now.

5

Patient Experience with Drugs over Time[1]

Only after a drug is launched and in use by patients over time does a full understanding of its benefits and risks emerge. However, the system for collecting and analyzing data on patient experiences with drugs, and for integrating that information back into the regulatory process, is seriously flawed, according to many of the workshop speakers and participants. While computerized patient and pharmacy order entry systems and other information technologies have the potential to improve the way we conduct postmarketing surveillance, the comments of participants suggest that these technologies have not yet lived up to that potential. There were repeated calls for integrating postmarketing data into the regulatory component of the life cycle (represented by the box in the lower left corner of Figure 5-1).

LIMITATIONS OF POSTMARKETING SURVEILLANCE

The challenge, according to Dr. Berger, is that once we leave the hypothesis-driven preclinical environment where we have a great deal of certainty about causality, we enter a world of observational studies where it is difficult to conclude with certainty that there may be causality. Several workshop participants commented on the failure to systematically

[1]This section is based on the presentations of J. Marc Overhage, Regenstrief Institute; Brian Strom, University of Pennsylvania; John Graham, RAND Corporation, and former Administrator, Office of Management and Budget, Office of Information and Regulatory Affairs.

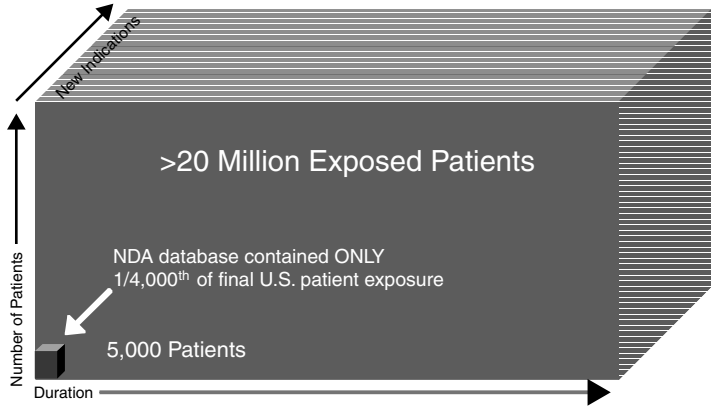

FIGURE 5-1 Learning about benefits and risks is a continuous process, creating a tremendous challenge with respect to updating benefit–risk assessments as postmarketing data accumulate.
SOURCE: From the presentation of discussion leaders Marc Berger, M.D., and Paul Seligman, M.D., MPH.

collect postmarketing safety data and the lack of confidence by many in the ability to monitor drugs in the postmarketing environment.

Dr. Strom discussed three primary postmarketing surveillance data sources and their limitations:

1. The Adverse Event Reporting System (AERS) has been the primary source of postmarketing information about drugs since the 1950s. Hundreds of thousands of adverse reaction reports are collected and analyzed annually. The system has seen very little improvement over time other than becoming computerized. Its major limitation is that it remains a collection of case reports that can signal problems, but cannot be used to draw conclusions.

2. Computerized claims or medical record systems, which are widely used and have been in existence since the late 1970s, include pharmacy, hospital, and physician claims reports sent to insurance carriers. Common identification numbers are increasingly being used to maximize the use of claims databases for research purposes. The Achilles heel of this type of system is physician reimbursement, which is based on visits rather than diagnosis. While hospitals and pharmacies must include diagnostic or drug identification information in claims forms, there is no incentive for physicians to do so.

3. Data collected de novo include datasets from either randomized trials or large observational studies. The problem with relying on this type of data is that they are expensive and time-consuming to collect. Once a drug reaches the market, the need to respond quickly to accusations about adverse reactions precludes this type of study.

In the discussion that followed Dr. Strom's presentation, there was a question about common events, such as heart attacks, and whether and how they would be detected through AERS, since that system seems to be more suited to detecting rare events. Dr. Strom replied that more common risks would need to be studied epidemiologically and through more active surveillance.

There was some question as to whether the quality of AERS data improves over time, because there has recently been a push to encourage consumers to send information. Dr. Galson remarked that, while AERS is not perfect, it is all that we have right now in terms of providing a system for patients and physicians to alert the FDA. In the future, with better electronic systems and a more comprehensive national healthcare information infrastructure (e.g., the Medicare system that links health outcomes with prescribing data), our dependence on AERS will decrease. Until that happens, although the quality of the data from consumer reports can be dubious, there is no real substitute for the information collected through AERS.

Dr. Strom agreed that AERS is irreplaceable today but disagreed with Dr. Galson's forecast that our dependence on it will decrease. He argued that automated data systems have existed for years and our dependence on AERS is no less now than it has been in the past. He further argued that with respect to adding data to AERS—more is not better. Smaller databases can allow for richer data extraction (by getting additional information about each case). In some countries, such as Sweden and Australia, where the number of reports is smaller, regulators have the ability to access much more detailed clinical information, which can be critical for accurately interpreting the results. If anything, increasing the size of the AERS database will result in people resorting to analyses based on the assumption that they are dealing with epidemiological data, which they are not.

There was some discussion about whether and how postmarketing information on risk and benefits can be incorporated into labels or made available in ways that allow physicians and other clinicians to use the information more effectively. Dr. Strom remarked that, first, given how our knowledge of both benefits and risks changes after marketing, comprehensive information isn't even available in many cases. Once this information does become available, given the mass of information, the

challenge will be to effectively utilize it. That, he argued, is a question of informatics. Our society is beginning to computerize its healthcare system and, in so doing, it is also building the capacity to collect and analyze large amounts of information in a way that will rapidly alert physicians and pharmacists to safety signals.

Finally, there were some comments made about how much of the discussion was focused on postmarket "surveillance" that perhaps ought to be focused on "data collection and analysis"; the issue of comparative effectiveness; the issue of polypharmacy, which is a key factor driving the discrepancy between efficacy and effectiveness but for which there is almost no data from an outcomes point of view; and the dearth of postmarketing data on pediatric drugs in particular. All of these omissions, Dr. Strom noted, relate to "the mission of the search." That is, how do we improve the use of drugs? He argued that by focusing on rare adverse reactions to new drugs, we are targeting the wrong question. Important public health questions are related to common adverse reactions to older drugs that are not being used optimally either by practitioners or by patients.

POSTMARKETING SURVEILLANCE WORKS: A CASE EXAMPLE

Dr. Overhage argued that both spontaneous reporting and active surveillance must be considered when thinking about how to adjust or modulate understanding of risk. Spontaneous reporting is invaluable because it is filtered (e.g., through astute physicians) and useful for identifying suggestive time relationships and plausible mechanisms. However its signal is low, with only about 10 percent of adverse events detected.[2] Active surveillance produces a stronger signal, and its larger numbers allow for relative risk calculations, better precision, and comparisons within or between drugs.

Dr. Overhage described a recent study demonstrating that both automated (computer database) and manual (chart review) active surveillance identify significantly more events than spontaneous reporting. Interestingly, however, there is not much overlap (Jha et al. 1998). While computerized surveillance is better than chart review for detecting drug interactions and other laboratory-based changes, it is not as good at detecting symptom-related mild adverse events. Also, while automated surveillance can reliably and consistently identify signals, only some of those signals are adverse events (Honigman et al. 2001).

He emphasized that the feasibility of utilizing properly collected routine clinical data for surveillance is based on data reuse. Collecting

[2]For example, see Classen et al. 1991.

data is difficult and expensive, so standardizing and employing those data for multiple purposes is important.

Dr. Overhage described his work with the Indiana Network for Patient Care, a regional health information exchange that has been in development for several years. The goal of that program is to develop an operational, sustainable statewide health information exchange that networks across all of the approximately 6,000 physician practices and hospitals in Indiana. The network relies on real-time clinical data augmented by claims data and defined signals that meet specific preset criteria, indicating that an adverse event *may* have happened. Signals are evaluated through a tiered, computer-assisted human review process. The success of the system thus far demonstrates that it is possible to capture and store population-based data in order to identify adverse events and update risk information on an ongoing basis. The signals can also be used to conduct nonrandomized observational studies designed to test prespecified hypotheses.[3]

Dr. Overhage was asked about the limitations of using postmarketing observational data to update benefit profiles, as well as risk profiles, for various therapies, compared to data collected from randomized control trials. He replied that the system does not collect a lot of those data and will probably not for some time.

When asked about cost, Dr. Overhage stated that the cost is related to the accuracy desired. If one is willing to be 95 percent accurate, but not perfect, the cost would not be excessive. Perfection, on the other hand, is very expensive. He reemphasized that data reuse is what makes this feasible. The fact that the data are collected not just for Phase IV surveillance but also for public health, quality improvement for payers, and so on, with each stakeholder investing, makes it affordable.

There was a question about whether it was possible to publish comparative evaluations of benefit–risk that would be directly useful to physicians and other front-line providers. It was suggested that if more patient information needs to be collected in order to do this, the pharmaceutical industry could be taxed to support the independent (and credible) organizations that would do the work. Dr. Overhage responded that, first, it was an issue of scale. The program (network) would need to be expanded. Second, many unanswered methodological questions remain as well as many lessons to be learned about how to use observational data (e.g., separating signals from noise). Third, presenting the data to physicians and patients is a challenge, because nobody knows how to organize and synthesize the data in a way that is usable for them.

A comment was made about the necessity of standardizing electronic medical records so that data can be pooled across the country and that

[3]For example, see Farwell et al. 2004 and Chalasani et al. 2004.

we must be very careful with algorithms—we need to develop and then test them. Dr. Overhage remarked that, yes, every network study involves tuning the algorithms (he called it the "musical model") for exactly that reason—to validate. He noted that the query tool of his system is very fast—it takes 15 to 20 minutes to query across 1.7 million patients. So the algorithm can be cycled and tuned very quickly. Moreover, the data-rich system can be used to address questions that may not be possible to address with smaller prospective or observational studies.

A comment was made that while the mining of more information may generate better hypotheses, it is not going to replace our need to do good experimentation in order to be really certain about benefit–risk. Others agreed that there are enormous challenges ahead, despite the optimism heard here and at so many other conferences about the future of fully interoperable automated electronic health records. First we need to solve the methodological problems (e.g., teasing apart the signal and noise for both benefit and risk) as well as data entry problems (e.g., nonstandardized coding, coding errors, and incomplete knowledge in many cases about why a drug was even prescribed).

It was noted that earlier in the day, Dr. Leiden had proposed a new paradigm for drug development that depends in large part on our ability to collect robust information in the postmarketing arena and be able to do experimental studies that involve randomization, or in some way classifying individuals into different groups, so that we can continue to collect good efficacy as well as safety information. Yet are the kinds of databases that Dr. Overhage accesses and structures the right venue for doing these kinds of studies? Do we need to think about other kinds of databases that one would have to construct in order to be able to do those rigorous studies? Dr. Overhage responded that if the databases provide 80 percent of the answer and that 80 percent is worthless without the remaining 20 percent, then no, we don't have the right information. There are no incentives to collect and align that other 20 percent. On the other hand, with carefully selected questions, appropriate things can be done with the data. While doing those things, we can build in that direction, but we need to ask our questions carefully because capturing data is expensive.

VALIDATING BENEFIT–RISK DATA DURING POSTAPPROVAL: LESSONS FROM THE OMB

Dr. Graham noted that, based on his experience at the U.S. Office of Management and Budget (OMB), agencies often have a very strong incentive to make their proposals look as good as possible, in order to get them approved. This leads to analytical practices that are "not always of ideal academic quality." For example, in deciding on an alternative,

agencies may compare their alternative with only one other option (e.g., a "do-nothing," or status quo, option). The challenge for OMB, therefore, is to persuade agencies to perform more serious analyses of a next-best alternative or a variant of the preferred alternative. When OMB pushes for these additional analyses, it often experiences pushback from the agencies that express concerns about limited time or resources. Dr. Graham remarked that the FDA probably experiences a similar problem. While manufacturers may present data comparing their proposed therapy to a placebo, the more important clinical questions may relate to whether the proposed therapy is superior to other treatments already on the market. The solution to this problem is not straightforward. If the FDA were to compel manufacturers to generate data on a broader range of alternatives, the cost and delays associated with FDA approval would increase significantly.

A better solution, Dr. Graham argued, would be to stimulate more research and analysis during the postapproval period. Echoing what other presenters had suggested, this postmarketing research should be conducted by a variety of sources. Dr. Graham suggested multiple organizations that compete with each other for the reputation of doing quality work. An expansion of university-based programs in pharmacoepidemiology and pharmacoeconomics, with a mix of government and industry funding, would be a useful step in the right direction.

Dr. Graham then discussed the validation of benefit and risk data after a regulatory decision has been made. In its most recent report to Congress *Validating Regulatory Analysis*, OMB assembled all 47 published case studies (out of more than 20,000 new regulations since 1981) in which benefit and cost estimates had been validated after the rule was promulgated (OMB 2005). Such a limited sample allows only limited insights, but it is nonetheless interesting to note that federal regulators exaggerated both benefits and costs in most cases. They exaggerated benefit because they wanted their product to look good. They exaggerated cost because they underestimated the creativity of the industry in finding ways to meet regulatory requirements at lower cost. The report highlights the need for a broader literature to allow us to validate preapproval benefit–risk estimates.

With respect to the FDA, are there numeric projections that are falsifiable? Could we perform validation analyses on this process? While it is not obvious that this can be done, the advantage of doing it would be a track record of better estimations of risk and benefit. By documenting systematic errors, it becomes feasible to improve future benefit–risk analyses and identify situations where adjustments need to be made. Ultimately, Dr. Graham's presentation raised concern about the lack of resources and incentives for following up on regulatory decisions.

6

Next Steps

Over the course of the workshop, participants generally agreed on several themes or points that are important to consider in improving our understanding of benefits and risks of pharmaceuticals:

- It is important in pharmaceutical benefit–risk analysis to provide patients and physicians with the best possible information for making informed decisions about the use of pharmaceuticals.
- It is important to employ quantitative and standardized approaches when trying to evaluate pharmaceutical benefit–risk. These approaches should augment rather than replace current regulatory approaches to pharmaceutical approval and labeling. More work needs to be done to develop and validate such tools.
- It is important to educate patients and physicians about the concepts of pharmaceutical benefit–risk and how these are assessed throughout the life cycle of a drug.
- It is important to develop and validate improved tools for communicating pharmaceutical benefit–risk information to patients and physicians.
- It is important to involve patients and physicians in the development of new tools for evaluating and communicating data concerning pharmaceutical benefit–risk.
- It is important to improve the current system for collecting postmarketing safety and efficacy data on marketed pharmaceuticals.

The workshop concluded with a discussion of possible next steps. Several suggestions were put forth:

- Develop an eight- to ten-page bulleted summary of facts and assumptions about pharmaceutical risk and benefit that the IOM or the Forum could use to educate legislators and others. This could also be posted on the web for physicians and patients.
- Design one or more pilot studies with the FDA to address some of the suggestions and considerations voiced at this meeting—for example, a study on utility-based analysis of benefit–risk for either an existing drug or a drug that is under FDA consideration. A second pilot could test the utility of one or more new patient–physician communication tools such as the Prescription Drug Facts Box. Adopting an experimental attitude would be a way to move forward several of the specific initiatives suggested by meeting participants.
- Plan follow-up meetings that focus on specific problems. For example, one meeting could address novel approaches to postmarketing surveillance and the limits of AERS, another might compare different quantitative tools for evaluating drug benefit–risk, and a third might address risk management plans and whether and how they should be submitted at the time of a new drug application.
- Encourage patient and physician involvement in future discussions.
- Incorporate pharmaceutical pricing in the discussion of benefit–risk analysis because, at least for legislators, cost is a critical element of the discussion.
- Avoid assigning blame among the various stakeholders involved in benefit–risk assessment because it damages public trust.
- Consider instituting citizen councils, as the United Kingdom's National Institute for Clinical Excellence did when faced with a similar crisis in public trust. Decisions to be made by the FDA regarding benefit–risk assessment could be laid out for the councils, who would then be asked how they value the options. Not only would this tactic add legitimacy to the decisions being made, council members could become champions for those decisions—and "the state of the science"—in the larger community.

Several participants suggested that there is a need for urgency in addressing these steps because of the imminent reauthorization of the Prescription Drug User Fee Act (PDUFA) and the possible enactment other potential drug safety bills.

References

Americans growing less confident in FDA's job in safety, poll shows. 2006. *The Wall Street Journal Online*, May 24.

Berry D, Gillie I, Forster M. 1997. What do patients want to know about their medications and what do doctors want to tell them? A comparative study. *Psychology of Health* 12:467–480.

Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. 2004. Patients with elevated liver enzymes are not at higher risk for statin hepatoxicity. *Gastroenterology* 126(5):1287–1292.

Cohen JT, Bellinger DC, Connor WE, Kris-Etherton PM, Lawrence RS, Savitz DA, Shaywitz BA, Teutsch SM, Gray GM. 2005. A quantitative benefit–risk analysis of changes in population fish consumption. *American Journal of Preventive Medicine* 29(4):325–334.

Classen DC, Pestotnik SL, Evans RS, Burke JP. 1991. Computerized surveillance of adverse drug events in hospital patients. *Journal of the American Medical Association* 266:2847–2851.

Edwards A, Elwyn G, Mulley A. 2002. Explaining risks: turning numerical data into meaningful pictures. *British Medical Journal* 324:827–830.

Farwell WR, Stump TE, Wang J, Tafesse E, L'Italien G, Tierney WM. 2004. Weight gain and new onset diabetes associated with olanzapine and risperidone. *Journal of General Internal Medicine* 19(12):1200–1205.

FDA. 2007. *FDA's Mission Statement*. [Online] Available: http://www.fda.gov/opacom/morechoices/mission.html [accessed May 31, 2007].

Gramling R, Irvin JE, Nash J, Sciamanna C, Culpepper L. 2004. Numeracy and medicine: key family physician attitudes about communicating probability with patients. *Journal of the American Board of Family Practice* 17:473.

Gray GM, Hammitt JK. 2000. Risk/risk trade-offs in pesticide regulation: an exploratory analysis of the public health effects of a ban on organophosphate and carbamate pesticides. *Risk Analysis* 20:665–680.

Honigman B, Less J, Rothschild J, Light P, Pulling RM, Yu T, Bates DW. 2001. Using computerized data to identify adverse drug events in outpatients. *Journal of the American Medical Informatics Association* 8:254–266.

IOM (Institute of Medicine). 2006. *Valuing Health for Regulatory Cost-Effectiveness Analysis*. Washington, DC: The National Academies Press.

Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vliet MV, Bates DW. 1998. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *Journal of the American Medical Informatics Association* 5:305–314.

National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process.* Washington, DC: National Academy Press.

National Research Council. 1999. *Health Effects of Exposure to Radon, BEIR VI.* Washington, DC: National Academy Press.

Nease Jr. RF, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Pryor D, Sox HC. 1995. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. *Journal of the American Medical Association* 273(15):1185–1190.

OMB (Office of Management and Budget). 2005. Validating Regulatory Analysis: 2005 Report to Congress on the Costs and Benefits of Federal Regulations and Unfunded Mandates on State, Local, and Tribal Entities. Washington, DC: OMB

Sheiner LB. 1997. Learning vs. confirming in clinical drug development. *Clinical Pharmacology and Therapeutics* 61:275–291.

Spiegel BM, Targownik L, Dulai GS, Gralneck IM. 2003. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Annals of Internal Medicine* 138(1):795–806.

Stossel TP. 2005. Regulating academic-industrial research relationships—solving problems or stifling progress? *New England Journal of Medicine* 353:1060–1065.

Strom BL. 2006. How the U.S. drug safety system should be changed. *Journal of the American Medical Association* 295:2072–2075.

Weinstein ND. 1999. What does it mean to understand a risk? Evaluating risk comprehension. *Journal of the National Cancer Institute* 25:15–20.

Woloshin S, Schwartz LM, Welch HG. 2004. The value of benefit data in direct-to-consumer drug ads. *Health Affairs* Suppl Web Exclusives: W4-234–W4-245.

A

Workshop Agenda

UNDERSTANDING THE BENEFITS AND RISKS OF PHARMACEUTICALS

May 30–31, 2006
NAS Keck Center
Room 100
500 Fifth Street NW
Washington, DC 20001

Tuesday, May 30, 2006

7:45 am **Breakfast**

8:15 am **Opening Remarks**

Workshop Co-Chairs

Steven Galson, M.D., M.P.H.
Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Jeffrey Leiden, M.D., Ph.D.
President and COO, Abbott Laboratories

Topic 1 ***What general frameworks are used to assess risk/benefit in non-pharmaceutical industries or organizations?***
(20 minute presentations)

8:45 am **Understanding the psychology of risk/benefit assessment**
Discussion Leader: Jeffrey Leiden, M.D., Ph.D.

Paul Slovic, Ph.D.
President, Decision Research

Peter Ubel, M.D.
Director, Center for Behavioral and Decision Sciences in Medicine, University of Michigan

Sheila Jasanoff, J.D., Ph.D.
Professor, John F. Kennedy School of Government, Harvard University

9:45 am **Discussion**

10:05 am **Break**

10:20 am **Assessing the effectiveness of risk/benefit algorithms from other industries**
Discussion Leader: Steven Galson, M.D., M.P.H.

Dennis Paustenbach, Ph.D.
President, ChemRisk

Jonathan M. Samet, M.D., M.S.
Professor and Chair, Department of Epidemiology, Johns Hopkins University

Joshua T. Cohen, Ph.D.
Lecturer, Tufts New England Medical Center

Richard Hall, Ph.D.
Vice President, Science and Technology (retired), McCormick & Company, Inc.

11:40 am **Discussion**

12:00 pm **Lunch**

12:45 pm **What are the challenges in effectively educating people about risk/benefit decisions?**
Discussion Leader: Jeffrey Leiden, M.D., Ph.D.

Hal Sox, M.D.
Editor, Annals of Internal Medicine

Isaac Lipkus, Ph.D.
Associate Research Professor, Psychiatry and Behavioral Sciences, Duke University

Steven Woloshin, M.D., M.S.
Professor of Medicine and Community and Family Medicine, Dartmouth University

2:05 pm **Discussion**

Topic 2 ***How do we currently assess risk/benefit ratios for pharmaceuticals?***
(20 minute presentations)

2:25 pm **Unique challenges for pharmaceuticals**
Discussion Leader: Steven Galson, M.D., M.P.H.

Steve Galson, M.D., M.P.H.
Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Brian Strom, M.D., M.P.H.
Chair, Department of Biostatistics and Epidemiology, University of Pennsylvania

3:05 pm **Discussion**

3:30 pm **Break**

3:45 pm **Advantages and drawbacks of the current system**
Discussion Leaders: Tim Franson, M.D., and Sandra Kweder, M.D.

Peter Barton Hutt, LL.B., LL.M.
Senior Counsel, Covington & Burling LLP

Peter A. Tollman, Ph.D.
Senior Vice President and Director, The Boston Consulting Group

David Slavin, M.D.
Executive Director, World Wide Development Business Innovations Unit, Pfizer Inc.

Brian Strom, M.D., M.P.H.
Chair, Department of Biostatistics and Epidemiology, University of Pennsylvania

5:05 pm **Discussion**

5:30 pm **Adjourn to Reception**

Wednesday, May 31, 2006

8:00 am **Breakfast**

Topic 3 ***How should we evaluate the risks and benefits of pharmaceuticals?***
(20 minute presentations)

Charge to the panel: What are the steps to adopt these new approaches for the drug review system? What are the areas of agreement? What additional work needs to be done?

8:30 am **Goals/objectives of future systems**
Discussion Leader: Jeffrey Leiden, M.D., Ph.D.

Jeffrey Leiden, M.D., Ph.D.
President and COO, Abbott Laboratories

Douglas Throckmorton, M.D.
Deputy Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Carl Spetzler, Ph.D., M.B.A.
Chairman, Strategic Decisions Group

9:30 am **Discussion**

9:50 am **Applicable systems from other industries**
Discussion Leader: Steven Galson, M.D., M.P.H.

Lynn Goldman, M.D., M.P.H.
Professor, Environmental Health Sciences, Johns Hopkins University

John Graham, Ph.D.
Former Administrator, Office of Management and Budget, Office of Information and Regulatory Affairs

10:30 am **Discussion**

11:00 am **Break**

11:15 am **What specific methodologies from other industries or academia are adaptable to the drug review system?**
Discussion Leaders: Jeffrey Leiden, M.D., Ph.D., and Sandra Kweder, M.D.

Alan Garber, M.D., Ph.D.
Professor of Medicine, Stanford University

Louis Garrison, Ph.D.
Professor of Pharmacy, University of Washington

11:55 am **Discussion**

12:20 pm **Lunch**

1:40 pm **How should we continuously update risk/benefit information with post-marketing data?**
Discussion Leaders: Mark Berger, M.D., and Paul Seligman, M.D., M.P.H.

J. Marc Overhage, M.D., Ph.D.
Chief Executive Officer, Indiana Health Information Exchange, Senior Investigator, Regenstrief Institute

2:00 pm **Discussion**

2:30 pm **Break**

2:40 pm **Presentation of Zometa as a case example**
Larry Lesko, Ph.D.
Director, Office of Clinical Pharmacology and Biopharmaceutics, U.S. Food and Drug Administration

3:00 pm **Discuss how new approaches could work with the case example (Zometa)**
(15 minute presentations)
Discussion Leader: Jeffrey Leiden, M.D., Ph.D.

Lisa Schwartz, M.D., M.S.
Associate Professor of Medicine and Community and Family Medicine, Dartmouth University

Kevin A. Schulman, M.D.
Professor of Medicine, Duke University

Mark Fendrick, M.D.
Professor, Department of Internal Medicine, University of Michigan

4:00 pm **Discussion**

4:35 pm **Next Steps**

5:30 pm **Adjourn**

B

Discussion Leader and Speaker Biographies

Marc L. Berger, M.D., obtained his M.D. from Johns Hopkins University School of Medicine. He completed an internal medicine residency at NYU–Bellevue Hospital in New York and a Liver Research Fellowship at the University of Texas Health Science Center at Dallas–Southwestern Medical School. Prior to joining Merck, he was on the faculty of the University of Cincinnati School of Medicine. While at Merck, Dr. Berger has held various positions of responsibility for Phase II to Phase IV clinical trials, outcomes research studies and disease management programs. He is currently Vice President of Outcomes Research and Management (ORM) in the US Human Health Division. Dr. Berger has co-authored numerous articles in outcomes research, health economics, and health policy. Currently, he is a member of the AHRQ Centers for Education and Research on Therapeutics (CERTs) Steering Committee, the CMS Medicare Coverage Advisory Committee (MCAC), and the writing committee for the AHRQ development of a handbook for *Registries for Evaluating Patient Outcomes.* He also serves on advisory boards for the Health Industry Forum and the Program on the Economic Evaluation of Medical Technology (PEEMT) at the Harvard Center for Risk Analysis, as well as the editorial advisory board of the journal *Value in Health*. Dr. Berger is a trustee of the Occupational and Environmental Health Foundation and the Merck Childhood Asthma Network, Inc. He holds appointments as Adjunct Senior Fellow at the Leonard Davis Institute of Health Economics at the University of Pennsylvania, Adjunct Professor in the Department of Health Policy and Administration at the University of North Carolina

at Chapel Hill School of Public Health, and Senior Scholar, Department of Health Policy, Jefferson Medical College.

Joshua T. Cohen, Ph.D., is a Lecturer at the Tufts New England Medical Center Institute for Clinical Research and Health Policy Studies, in the Center for the Evaluation of Value and Risk. Dr. Cohen's research focuses on the application of decision analytic techniques to public health risk management problems with a special emphasis on the proper characterization and analysis of uncertainty. His work covers a range of issues, including cell phone use while driving, alternative fuels for transit buses and school buses, tradeoffs between the nutritional benefits of fish and resulting exposure to mercury, and the risks associated with bovine spongiform encephalopathy in the United States. Dr. Cohen currently serves on a National Academy of Sciences committee charged with reviewing the U.S. Environmental Protection Agency (EPA)'s risk assessment of dioxin, and on the EPA's Clean Air Science Advisory Committee that is now reviewing the Agency's latest air quality criteria document for lead. He received both his Ph.D. in Decision Sciences and his B.A. in Applied Mathematics from Harvard University.

A. Mark Fendrick, M.D., is a Professor of Internal Medicine in the School of Medicine and a Professor of Health Management and Policy in the School of Public Health at the University of Michigan. Dr. Fendrick received a bachelor's degree in economics and chemistry from University of Pennsylvania and his medical degree from Harvard. Dr. Fendrick completed his residency in internal medicine at the University of Pennsylvania where he was a fellow in the Robert Wood Johnson Foundation Clinical Scholars Program. He currently directs the Health Services Research Core Laboratory and is co-director of the recently established Center for Value-Based Insurance Design at the University of Michigan. Dr. Fendrick's research focuses on the clinical and economic assessment of medical interventions with special attention to how technological innovation influences clinical practice and impacts health care systems. He has authored over 200 articles and book chapters and lectures frequently on the health and cost implications of medical interventions to diverse audiences around the world. Dr. Fendrick remains clinically active in the practice of general internal medicine. He is the co-editor in chief of the *American Journal of Managed Care* and is an editorial board member for 3 additional peer-reviewed publications. His perspective and understanding of clinical and economic issues have fostered collaborations with numerous government agencies, health plans, professional societies, and health care companies. He serves on the Medicare Coverage Advisory Committee.

Timothy R. Franson, M.D., is currently Vice President of Global Regulatory Affairs for Lilly Research Laboratories and is also an Assistant Professor of Medicine at Indiana University School of Medicine. He received his undergraduate degree in Pharmacy (B.S. Pharm, honors) at Drake University, his M.D. degree (James Scholar, with honors) at the University of Illinois, and completed internal medicine training at the University of Iowa, followed by a fellowship in Infectious Diseases and Epidemiology at the Medical College of Wisconsin. Dr. Franson is Board Certified in Internal Medicine and Infectious Diseases. He was Assistant Professor of Medicine and Hospital Epidemiologist at the Medical College of Wisconsin where he was a National Institutes of Health (NIH) funded investigator and a member of the State of Wisconsin's Governors Task Force on AIDS. He joined Eli Lilly and Company in 1986, where he has previously served as Director of Anti-Infectives; Group Medical Director, Europe (based in the United Kingdom); Executive Director of Health Economics Research and Decision Sciences, Executive Director of Regulatory Affairs responsible for North American Regulatory, Chemistry Manufacturing Control, Planning & Global Operations (safety, labeling, medical information, registration and submissions) and from 1997–2003, Vice President of Clinical Research and Regulatory Affairs-US. In 2002, Dr. Franson received the Lilly Chairman's Ovation Award.

Steven Galson, M.D., M.P.H., was named Director of the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA) in July 2005. He provides leadership for the Center's broad national and international programs in pharmaceutical regulation. Dr. Galson began his Public Health Service (PHS) career as an epidemiological investigator at the Centers for Disease Control after completing a residency in internal medicine at the Hospitals of the Medical College of Pennsylvania. He has held senior-level positions at the Environmental Protection Agency, the Department of Energy where he was the Chief Medical Officer, and the Department of Health and Human Services. Prior to his arrival at FDA, Dr. Galson was the Director of the Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, at the EPA. Dr. Galson joined FDA in April 2001 as the CDER Deputy Director. Dr. Galson is the recipient of numerous PHS awards, including the Outstanding Service Medal for his leadership and management of CDER while serving as Acting Center Director from November 2001 to February 2002. He is also the recipient of three Secretary of Energy Gold Awards. Dr. Galson is a board member of the National Board of Medical Examiners and a regular peer reviewer for medical journals. Dr. Galson holds a B.S. from Stony Brook University, an M.D. from Mt. Sinai School of Medicine and a M.P.H. from the Harvard School

of Public Health. He is Board Certified in Preventive Medicine & Public Health and Occupational Medicine.

Alan M. Garber, M.D., Ph.D., is the Henry J. Kaiser Jr. Professor and a Professor of Medicine at Stanford University, where he is also Professor of Economics, Professor of Health Research and Policy, and Professor of Economics in the Graduate School of Business (courtesy). He has been director of both the university's Center for Health Policy and the Center for Primary Care and Outcomes Research at the School of Medicine since their founding. He is also a Staff Physician at the Veterans Affairs Palo Alto Health Care System, Associate Director of the VA Center for Health Care Evaluation, and Research Associate and Director of the Health Care Program of the National Bureau of Economic Research (NBER). After graduating from Harvard College summa cum laude, Dr. Garber received his Ph.D. in economics from Harvard and an M.D. with research honors from Stanford, and completed his residency in Medicine at Brigham and Women's Hospital. He is the recipient of numerous honors and awards, including the Young Investigator Award of the Association for Health Services Research (now AcademyHealth) and the Henry J. Kaiser Family Foundation Faculty Scholarship in General Internal Medicine. He is a member of the national Blue Cross and Blue Shield Association Medical Advisory Panel and serves as their Scientific Adviser, and a member of the American Society for Clinical Investigation, the Association of American Physicians, the Institute of Medicine of the National Academy of Sciences, and the National Advisory Council on Aging (National Institutes of Health). He is the Chair of the Medicare Coverage Advisory Committee (Centers for Medicare and Medicaid Services). Dr. Garber's research is directed toward methods for improving health care delivery and financing, particularly for the elderly, in settings of limited resources. He has developed methods for determining the cost-effectiveness of health interventions, and he studies ways to structure financial and organizational incentives to ensure that cost-effective care is delivered. In addition, his research explores how clinical practice patterns and health care market characteristics influence technology adoption, health expenditures, and health outcomes in the United States and in other countries.

Louis Garrison, Ph.D., joined the faculty in the Pharmaceutical Outcomes Research & Policy Program in the Department of Pharmacy at the University of Washington in 2004. For the previous 12 years, he worked as an economist in the pharmaceutical industry. Most recently, he was Vice President and Head of Health Economics & Strategic Pricing in Roche Pharmaceuticals, and was based in Basel, Switzerland, in 2002–2004. He oversaw the development of the economic and pricing strategies, and

research plans for all Roche compounds. Prior to this, he was Director of the Project HOPE Center for Health Affairs. In eight years there, Dr. Garrison worked on a wide variety of health policy issues, including studies of health care reform both in the United States and overseas. Before this, he worked at the Battelle Human Affairs Research Centers in Seattle, where he carried out studies of the adequacy of physician manpower supply and the cost-effectiveness of kidney and heart transplantation. He received a B.A. in economics from Indiana University, and a Ph.D. in economics from Stanford University. Dr. Garrison's research interests include national and international health policy issues related to insurance, pricing, and reimbursement, as well as the economic evaluation of pharmaceuticals and diagnostics, particularly for organ transplantation, renal disease, influenza, and cancer.

Lynn R. Goldman, M.D., M.P.H., a pediatrician and epidemiologist, is Professor of Environmental Health Sciences at Johns Hopkins University Bloomberg School of Public Health, as well as chair of the Program in Applied Public Health. At Hopkins, she is the co-principal investigator for PACER (the Center for the Study of Preparedness and Critical Event Response) and researches impacts of environmental exposures on children's health. An expert in chemicals and pesticide policy, she previously served as assistant administrator at the U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Dr. Goldman is a fellow of the American Academy of Pediatrics. She currently is a member of the Institute of Medicine Health Sciences Policy Board and Vice Chair of the Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine and has served on multiple expert committees for the National Academies of Sciences and the government. She received the Woodrow Wilson Award for Distinguished Government Service from the Johns Hopkins University Alumni Association and the UC Berkeley, School of Public Health Alumna of the Year Award.

John D. Graham, Ph.D., was born (1956) and raised in Pittsburgh, PA, a son of an accomplished steel industry executive. He earned his B.A. (politics and economics) at Wake Forest University (1978) where he won national awards as an intercollegiate debater. He earned his M.A. degree in public policy at Duke University (1980) before serving as staff associate to Chairman Howard Raiffa's Committee on Risk and Decision Making of the National Research Council/National Academy of Sciences. His Carnegie-Mellon University Ph.D. dissertation on automobile safety, written at the Brookings Institution, was cited in pro-airbag decisions by the U.S. Supreme Court (1983) and by Secretary of Transportation

Elizabeth Dole (1985). Dr. Graham joined the Harvard School of Public Health as a post-doctoral fellow in 1983 and as an assistant professor in 1985. He taught the methods of decision analysis and cost-benefit analysis to physicians and graduate students in public health. His prolific writings addressed both the analytic and institutional aspects of lifesaving policies. Dr. Graham earned tenure at Harvard in 1991 at the age of thirty-four. From 1990 to 2001 Dr. Graham founded and led the Harvard Center for Risk Analysis (HCRA). By raising over $10 million in project grants and philanthropic contributions, Dr. Graham helped support eight new faculty positions and dozens of post-doctoral and doctoral students. By 2001 HCRA had become internationally recognized for analytic contributions to environmental protection, injury prevention, and medical technology innovation. In 1995 Dr. Graham was elected President of the Society for Risk Analysis, an international membership organization of 2,400 scientists and engineers. Dr. Graham reached out to risk analysts in Europe, China, Japan and Australia as he helped organize the first World Congress on Risk Analysis (Brussels, 2000). Dr. Graham became widely known to the public and opinion leaders through his entertaining speeches about why Americans are both paranoid and neglectful of risks in their daily lives. He made several prime-time television appearances, including John Stoussel's ABC special, "Are We Scaring Ourselves to Death?" and has spoken frequently to groups of reporters, business leaders, and government officials. He has delivered invited testimony to numerous House and Senate Committees, state and federal agencies, and the European Commission and Parliament. The late Senator Daniel Patrick Moynahan (D-NY) praised Dr. Graham as a pioneer in bringing the insights from risk analysis to federal clean-air legislation. In March 2001 President Bush nominated Dr. Graham to serve as Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget. He was confirmed by the Senate in July 2001. Located in the Executive Office of the President, this small office of 50 career policy analysts oversees the regulatory activities of the federal government. In this capacity, Dr. Graham has worked to slash the growth of regulatory costs by 70 percent while encouraging good regulations that save lives, prevent disease, and protect the environment in a cost-effective manner. Dr. Graham is currently Dean of the Frederick Pardee RAND Graduate School at the RAND Corporation in Santa Monica, California. In this role, Dr. Graham leads the nation's largest doctoral training program in public policy analysis. He also holds a Chair in Policy Analysis which supports his research activities.

Richard Hall, Ph.D., was with McCormick & Company for 38 years, retiring in 1988 as Vice-President—Science and Technology. He has served on numerous NRC and IOM Boards and Committees including the Food

and Nutrition Board. He is a Past President of the International Union of Food Science and Technology, a fellow of the AAAS, the Institute of Food Technologists, and a Distinguished Fellow of the Toxicology Forum.

Peter Barton Hutt, LL.B., LL.M., is a senior counsel in the Washington, D.C., law firm of Covington & Burling specializing in food and drug law. He graduated from Yale College and Harvard Law School and obtained a Master of Laws degree in Food and Drug Law from NYU Law School. Mr. Hutt served as Chief Counsel for the Food and Drug Administration during 1971–1975. He is the co-author of the casebook used to teach food and drug law throughout the country, and has published more than 175 book chapters and articles on food and drug law and health policy. He teaches a full course on this subject during Winter Term at Harvard Law School and has taught the same course during Spring Term at Stanford Law School. Mr. Hutt has been a member of the Institute of Medicine since it was founded in 1971. He serves on academic, philanthropic, and venture capital advisory boards, and the boards of startup biotechnology companies. He currently serves on the Panel on the Administrative Restructuring of the National Institutes of Health, the Working Group to Review Regulatory Activities Within the Division of AIDS of the National Institute of Allergy and Infectious Diseases, and the Board of Directors of the AERAS Global TB Vaccine Foundation. In April 2005, Mr. Hutt was presented the FDA Distinguished Alumni Award by FDA Commissioner Crawford. In May 2005, he was given the Lifetime Achievement Award by the Foundation for Biomedical Research, for research advocacy.

Sheila Jasanoff, J.D., Ph.D., is Pforzheimer Professor of Science and Technology Studies at Harvard University's John F. Kennedy School of Government. She has held academic positions at Cornell, Yale, Oxford, Cambridge, Kyoto, and the Berlin Institute for Advanced Study. Her research centers on the role of science and technology in the law, politics, and public policy of modern democracies. Her books include *Controlling Chemicals* (1985), *The Fifth Branch* (1990), *Science at the Bar* (1995), and *Designs on Nature* (2005). Dr. Jasanoff has served on the Board of Directors of the American Association for the Advancement of Science and as President of the Society for Social Studies of Science.

Sandra Kweder, M.D., is Deputy Director of the FDA's Office of New Drugs (OND), with oversight of over 700 scientific staff who review all investigational drug products and new drug marketing applications, including those for therapeutic biologics. She also directly oversees special project teams in OND, including a team devoted to development of standards for study endpoints and labeling claims, particularly patient

reported outcomes; and a team dedicated to developing new regulations and scientific standards for studying and labeling drugs for safe use in pregnancy and lactation. She has recently taken on oversight of the FDA's Pediatrics Drug Development Team. Dr. Kweder is board certified in Internal Medicine and continues to practice and teach on a weekly basis at the Uniformed Services University and National Naval Medical Center. She has a special interest and fellowship training in Obstetric Medicine, the care of pregnant women with complicated medical conditions. She has had previous positions in the FDA in the areas of infectious disease products and in postmarketing safety.

Jeffrey M. Leiden, M.D., Ph.D., was president and chief operating officer, Pharmaceutical Products Group at Abbott until March, 2006. Prior to Abbott, Leiden served as the Elkan R. Blout professor of biological sciences, Harvard School of Public Health and professor of medicine, Harvard Medical School. Prior to that, he was the Frederick H. Rawson Professor of Medicine and Pathology and Chief of the Section of Cardiology at the University of Chicago. His extensive business and consulting experience includes both the pharmaceutical and medical device arenas. He was a founder of Cardiogene, Inc., a biotechnology company specializing in cardiovascular gene therapy. Dr. Leiden currently serves on the board of directors of TAP Pharmaceutical Products, Inc., the Ravinia Festival, the PENN Medicine Board at the University of Pennsylvania, and A*Star. He is a member of the American Society of Clinical Investigation and the American Association of Physicians, and a fellow of the American Academy of Arts and Sciences. He was elected to the Institute of Medicine of the National Academy of Sciences in 2001. Leiden earned a bachelor's degree in biological sciences, a doctorate in virology, and a medical degree, all from the University of Chicago.

Lawrence J. Lesko, Ph.D., F.C.P., has been the Director of the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) since 1995. The main focus of the Office of Clinical Pharmacology is the translational analysis of dose-response and PK-PD data for the purposes of optimizing dosing and the benefit/risk ratio of FDA-approved drugs, the use of PK and biomarkers to assist in dosing adjustments for drug-drug interactions, special populations (e.g., renal patients), and other patient subsets defined by pharmacogenomics, individualization of drug therapy using plasma drug levels, and the application of quantitative methods such as disease state progression models and simulations to design clinical trials. Outside the FDA, Dr. Lesko has served as President of the American College of Clinical Pharmacology from 2004–2006. Prior to joining the FDA, Dr. Lesko

was a faculty member in academia for over 15 years, most recently at the University of Maryland. He has directed the clinical pharmacology laboratory at the University of Massachusetts Medical Center, and was Vice-President of PharmaKinetics Laboratories, a Baltimore-based contract research organization. He has been appointed as an adjunct professor at the University of Florida and at the University of Southern California in the Colleges of Pharmacy where he lectures and interacts with graduate students. Dr. Lesko is an American Association of Pharmaceutical Scientist (AAPS) Fellow and is Board Certified in Clinical Pharmacology by the American Board of Clinical Pharmacology. He has received the 2007 Rawls–Palmer Progress in Medicine Award from the American Society of Clinical Pharmacology and Therapeutics, the 2007 University of North Carolina Institute for Pharmacogenomics and Individualized Therapy for public service and clinical science, and will receive the Nathaniel T. Kwit Memorial Distinguished Service Award from the American College of Clinical Pharmacology in September 2007 for his contributions to the field of clinical pharmacology. He is a member of the editorial board of several prestigious journals including the *Journal of Clinical Pharmacology*. He has over 145 publications in peer-reviewed journals and is a frequent invited speaker nationally and internationally.

Isaac Lipkus, Ph.D., a health psychologist, is an Associate Professor and Chief of the Behavioral Branch within Duke University Medical Center's Program of Cancer Prevention, Detection and Control. He is nationally and internationally known as an expert in the area of risk communication, and has published over 75 articles in the leading health communication journals. He is Director of the acclaimed Duke University Medical Center's Risk Communication Lab (RCL). The RCL is devoted to developing novel persuasive and educational health communications generally and risk communication approaches specifically to affect preventative behaviors (e.g., diet, exercise, smoking cessation), cancer screening (e.g., breast and colorectal cancer), and medical decision making (e.g., breast cancer treatment, chemoprevention for breast cancer). These laboratory and randomized field trial studies, which now total over 30 studies involving over 2,600 participants of varied backgrounds, have tested optimal approaches for communicating cancer risks utilizing several media variables including different numerical, verbal and visual formats. His research also includes testing new frontiers of genetic risk communication (e.g., how genetic susceptibility affects smoking cessation)—he currently serves as a consultant to the National Human Genome Research Institute in their efforts to develop effective genetic risk communications. Overall, his research programs have resulted in several funded initiatives—approximately four million dollars in direct grant support and

about two million dollars in indirect grant support—primarily from the Department of Defense and the National Cancer Institute. Dr. Lipkus serves on various editorial boards and regularly consults with the leading health organizations in the country. In addition to being a frequently-invited speaker at several universities and research institutes, Dr. Lipkus has taught graduate seminars in risk communication and persuasion, among other topic areas.

J. Marc Overhage, M.D., Ph.D., is associate professor of medicine at the Indiana University School of Medicine, senior investigator at the Regenstrief Institute, and President and CEO of the Indiana Health Information Exchange. Dr. Overhage received his BA with high honors in physics from Wabash College, his Ph.D. in biophysics, and M.D. from Indiana University School of Medicine. Dr. Overhage was a resident in internal medicine, a medical informatics and health services research fellow and then chief medical resident at the Indiana University School of Medicine. Dr. Overhage has over 25 years of computing experience, including developing one of the earliest commercial object-oriented database systems. Over the last 10 years, he has been developing a regional health information exchange to integrate flows of clinical information between public health providers and other clinicians: making immunization registry data from public health department available to providers, creating regional electronic laboratory reporting, implementing and studying reminders to emergency medicine physicians to screen for selected conditions during outbreaks, and, most recently, working with Dr. Shaun Grannis to create the Public Health Electronic Syndromic Surveillance system for the state of Indiana. He has contributed to the development and implementation of the clinical data standards that underlay the Public Health Information Network and tested these standards in hospitals across the country. Dr. Overhage is a fellow of the American College of Medical Informatics and the American College of Physicians. He received the Davies Recognition Award for Excellence in Computer-Based Patient Recognition for the Regenstrief Medical Record System.

Dennis J. Paustenbach, Ph.D., is currently the President of ChemRisk, a human and ecological risk assessment consulting firm with four offices nationwide. He was previously the President of McLaren-Hart, a 600 person consulting environmental engineering firm and was a Vice President at Exponent (formerly Failure Analysis Associates). He was the founder of ChemRisk, the largest risk-assessment consulting firm in the United States during the 1990s and has resurrected the firm as of June 2003. He earned a BS in Chemical Engineering, an M.S. in industrial hygiene/toxicology, and a Ph.D. in Environmental Toxicology. He is board-certified in toxicology,

industrial hygiene, and safety and has more than 20 years of experience in risk assessment, environmental engineering, ecotoxicology, and occupational health. Dr. Paustenbach has specialized in exposure assessment and dose reconstruction for much of the past 15 years and has published about 40 articles and 7 book chapters on the topic. He has presented guest lectures and short courses on exposure assessment throughout the United States and at least five other countries. He has been an adjunct professor at several universities and was a visiting scholar at the Center for Risk Analysis at Harvard. Dr. Paustenbach has directed consulting activities for nearly 700 risk assessments and has published more than 250 peer-reviewed manuscripts in this and related fields. He is the editor of the most popular textbook on risk assessment, *Human and Ecological Risk Assessment: Theory and Practice.* Dr. Paustenbach was identified as the best Risk Practitioner within the SRA in 1998 and was awarded the Arnold J. Lehman award by the Society of Toxicology in 2002 in recognition of his contributions to the field of risk assessment. He is the founding editor of the *Journal of Children's Health*.

Jonathan M. Samet, M.D., M.S., pulmonary physician and epidemiologist, is currently Professor and Chairman of the Department of Epidemiology of the Johns Hopkins Bloomberg School of Public Health. His career has centered on epidemiologic research on threats to public health and using research findings to support policies that protect population health. His research has addressed indoor and outdoor air pollution, smoking, radiation risks, cancer etiology and outcomes, and sleep. Dr. Samet received a Bachelor's degree from Harvard College, an M.D. degree from the University of Rochester School of Medicine and Dentistry, and a M. S. degree in epidemiology from the Harvard School of Public Health. From 1978 through 1994, he was in the Department of Medicine at the University of New Mexico. Dr. Samet has participated in diverse activities related to translation of scientific evidence into public policy. He has served as author and editor for Surgeon General's Reports on smoking and testified against the tobacco industry in litigation brought by Minnesota and the Department of Justice. He has served on the EPA Science Advisory Board and was Chairman of the Biological Effects of Ionizing Radiation (BEIR) Committee VI and the Committee on Research Priorities for Airborne Particulate Matter of the National Research Council (NRC). He presently chairs NRC's Board on Environmental Studies and Toxicology (BEST). He has served on numerous advisory and review groups for the NIH. He has long been active in ATS, chairing the EOH Assembly, and participating in preparing many ATS statements and in the international respiratory epidemiology courses. He was Associate Editor for the *American Review of Respiratory Disease*. He has served on ALA committees of the concerned

with air pollution issues. He has also been president of the Society for Epidemiologic Research and the American College of Epidemiology. He was elected to the Institute of Medicine in 1997, and is an Honorary Fellow of the American College of Chest Physicians. Other honors include the Surgeon General's Medallion, the Prince Mahidol Award, the Harvard School of Public Health Alumni Award of Merit and the George W. Comstock Award from the Maryland Thoracic Society.

Kevin A. Schulman, M.D., M.B.A., is professor of medicine and vice chair for business affairs in the Department of Medicine in the Duke University School of Medicine. He also serves as director of the Center for Clinical and Genetic Economics at the Duke Clinical Research Institute and as professor of business administration, director of the Health Sector Management Program, and director of the Center for the Study of Health Management in The Fuqua School of Business at Duke University. Dr. Schulman's research centers on three broad themes: economic evaluation in clinical trials; health services research, including access to care and the impact of managed care on clinical practice; and clinical decision making, especially the assessment of decision making for patients with life-threatening diseases. Dr. Schulman has written extensively on his research topics, including peer-reviewed publications in the *New England Journal of Medicine*, the *Journal of the American Medical Association*, and *Annals of Internal Medicine*. He is currently a member of the editorial/advisory boards of seven journals, including the *American Journal of Medicine*, the *American Heart Journal*, *Health Services Research*, and *Value in Health*. Dr. Schulman also holds appointments in the Duke Center for Clinical Health Policy and the Durham VA Health Services Research Unit.

Lisa M. Schwartz, M.D., M.S., is a general internist at the White River Junction Veterans Administration in Vermont and co-director of the VA Outcomes Group, and an associate professor of medicine and community and family medicine at Dartmouth Medical School. Dr. Schwartz's work (in collaboration with Steven Woloshin) focuses on improving the communication of medical information to patients, physicians, journalists, and policymakers, has appeared in leading medical journals. Their work has focused on creating and testing practical ways to overcome two important barriers to good communication: (1) many people (patients, providers, journalists) are limited in their ability to interpret medical data; and (2) exaggerated and incomplete health messages are common. To this end, they are developing and testing material to help people understand medical statistics and the benefits and harms of prescription drugs, teach several medicine in the media workshops for journalists and write an occasional series for the *Washington Post* entitled "Healthy Skepticism."

Paul J. Seligman, M.D., M.P.H., current serves as the Associate Director for Safety Policy and Communication in the FDA's Center for Drug Evaluation and Research. He previously directed the Office of Pharmacoepidemiology and Statistical Science responsible for FDA's post-marketing drug surveillance, epidemiology and biostatistics programs. Prior to joining the FDA in July 2001, Dr. Seligman served as the Deputy Assistant Secretary for Health Studies at the Department of Energy where he was responsible for occupational medicine, health surveillance and epidemiology related to nuclear weapons production nationally and internationally. In 1994, Dr. Seligman was an American Political Science Association Congressional Fellow working in the office of Senator Paul Wellstone on the health care reform legislation. From 1983–1993, he worked at the Centers for Disease Control (CDC)/National Institute for Occupational Safety and Health (NIOSH) serving as an Epidemic Intelligence Officer, a Preventive Medicine Resident on assignment of the Ohio Department of Health, and as Chief of the Medical Section of NIOSH's Surveillance Branch. Prior to joining CDC, he completed a primary care internal medicine residency at The Cambridge Hospital in Cambridge, Massachusetts. From 1974–1976, he served as a Peace Corps volunteer in Kenya. Dr. Seligman is a commissioned officer in the U.S. Public Health Service. He holds an M.D. degree from the University of California, Davis, an M.P.H. in industrial health from the University of Michigan, and a B.S. in chemistry from Yale University. He is board certified in internal medicine, occupational medicine, and public health and general preventive medicine. He is the author and co-author of numerous articles and book chapters focusing on work-related injuries and illnesses, including occupational lead exposures and lead poisoning, skin disorders, carpal tunnel syndrome, and public health surveillance.

David E. Slavin, M.D., MFOM, is the Executive Director of the Business Innovation Unit (BIU), World Wide Development, Pfizer Global Research and Development. Since joining Pfizer, Dr. Slavin has been Global Head of Risk Technology within Clinical Technology, directing applied risk research to address the current societal trend towards risk aversion and precaution, by studying risk perception, trust and tolerability of risk. Most recently, he has been examining new opportunities for business improvements, value creation and value protection in the context of future healthcare paradigms. Dr. Slavin trained both as a family practitioner and occupational physician. Whilst in the Royal Navy Submarine Service he was deputy nuclear safety regulator for the UK Ministry of Defense and on exchange, the Principal Investigator for a U.S. Navy program involved in submarine atmosphere safety. These different industries required techniques, principles and strategies to answer the "how safe is safe enough?"

question and to place the answers in a risk informed context. Dr. Slavin is based in Sandwich, UK, for this global position.

Paul Slovic, Ph.D., is president of Decision Research and a professor of psychology at the University of Oregon. He studies human judgment, decision making, and risk analysis, and has published extensively on these topics. Dr. Slovic received a B.A. degree from Stanford University, M.A. and Ph.D. degrees from the University of Michigan, and honorary doctorates from the Stockholm School of Economics and the University of East Anglia. Dr Slovic has served on numerous advisory committees of the National Research Council/National Academy of Sciences, including the committees that wrote *Risk Assessment in the Federal Government: Managing the Process* (1983) and *Understanding Risk: Decision Making in a Democratic Society* (1996).

Harold C. Sox, M.D., graduated from Stanford University (B.S. physics) and Harvard Medical School. After serving as a medical intern and resident at Massachusetts General Hospital, he spent two years doing research in immunology at the National Institutes of Health and three years at Dartmouth Medical School, where he served as chief medical resident and began his studies of medical decision making. He then spent fifteen years on the faculty of Stanford University School of Medicine, where he was the chief of the division of general internal medicine and director of ambulatory care at the Palo Alto VA Medical Center. In 1988 he returned to Dartmouth where he served for thirteen years as Joseph M. Huber Professor of Medicine and chair of the department of medicine. He became the Editor of the *Annals of Internal Medicine* in 2001. Dr. Sox was the President of the American College of Physicians during 1998–1999. He chaired the U.S. Preventive Services Task Force from 1990 to 1995, the Institute of Medicine Committee to Study HIV Transmission through Blood Products, and the Institute of Medicine Committee on Health Effects Associated with Exposures Experienced in the Gulf War. He chaired the Medicare Coverage Advisory Committee of the Center for Medicare Services from 1999 to 2003 and served on the Report Review Committee of the National Research Council from 2000 to 2005. He was elected to the Institute of Medicine of the National Academies in 1993 and to fellowship in the American Association for the Advancement of Science in 2002. His books include *Medical Decision Making*, *Common Diagnostic Tests: Selection and Interpretation*, and *Graduate Education in Internal Medicine: a Resource Guide*.

Carl C. Spetzler, Ph.D., is chairman of Strategic Decisions Group (SDG). Specializing in strategy development, business innovation, and strategic

change management, Dr. Spetzler has developed creative business strategies for major financial institutions, capital-intensive companies, high-technology manufacturers, and systems businesses. Over the past 20 years, he has been a leader in designing an innovative strategy development process that helps corporate leaders cope with the lack of explicit strategic alternatives, deal with the complexities of uncertainty and risk over long time horizons, and achieve lasting change. In addition to serving as the chairman of the board for SDG, Dr. Spetzler works with top management and boards of directors to improve the quality of decisions. His methods stress that boards be collaboratively engaged in a few truly strategic decisions rather than simply serve in an approval role on a myriad of items. Before the founding of SDG, Dr. Spetzler directed the Financial Industries and Strategic Methodologies Center at SRI International. He received an M.B.A. and a Ph.D. in economics and business administration and BS in chemical engineering from the Illinois Institute of Technology (IIT). He serves on the boards of IIT and the Decision Education Foundation, a nonprofit organization dedicated to improving the decision-making skills of youth. In 2004, Dr. Spetzler received The Ramsey Medal, the highest honor awarded by the Decision Analysis Society of INFORMS for lifetime contributions to the field.

Brian L. Strom, M.D., M.P.H., is the George S. Pepper Professor of Public Health and Preventive Medicine at the University of Pennsylvania. He is Founding Director of the Center for Clinical Epidemiology and Biostatistics. The mission of the Center is to improve the health of the public by linking epidemiology, biostatistics, and clinical medicine, bringing epidemiologic research methods to clinical research, clinical insight to epidemiologic research, and an understanding of research methodology to clinical medicine. Since its inception in 1993, the Center has grown to more than 160 faculty members, with an annual budget exceeding $50 million. Dr. Strom earned his M.D. degree from Johns Hopkins University and his M.P.H. degree in epidemiology from the University of California at Berkeley. Dr. Strom also serves as Chair of the Department of Biostatistics and Epidemiology and has appointments in the departments of Medicine and Pharmacology. Recently, he was appointed Associate Vice Dean of the University of Pennsylvania School of Medicine and Associate Vice President for Strategic Integration for the University of Pennsylvania Health System. While Dr. Strom's research interests span many areas of epidemiology, his major career interest is pharmacoepidemiology, and he has written the major textbook in this field, now going into its fourth edition. In addition, he has more than 400 publications. Editor for the Americas for *Pharmacoepidemiology and Drug Safety*, Dr. Strom served on the Drug Safety and Risk Management Advisory Committee for the United States

Food and Drug Administration. He was previously President of the International Society for Pharmacoepidemiology. He is the immediate past President of the Association for Clinical Research Training. He was a member of the Board of Regents of the American College of Physicians, the Board of Directors of the American Society for Clinical Epidemiology and Therapeutics, and the Board of Directors of the American College of Epidemiology. A member of the Institute of Medicine of the National Academy of Sciences, he chaired the institute's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine and was recently Chair of its Committee on Smallpox Vaccine Program Implementation. Among his many honors is the 2003 Rawls–Palmer Progress in Medicine Award from the American Society of Clinical Pharmacology and Therapeutics.

Douglas C. Throckmorton, M.D., is the Deputy Director in the Center for Drug Evaluation and Research at the FDA. As a physician, he is Board-Certified in Internal Medicine and Nephrology, having received his training at Case Western Reserve University and Yale University. He practiced medicine at the Medical College of Georgia in Augusta, Georgia, until coming to the FDA in 1997. He began his career at the FDA in the Division of Cardio-Renal Drug Products, first as a Medical Reviewer, then as the Deputy Division Director and from 2002 until 2005 as the Division Director.

Peter A. Tollman, Ph.D., is a senior vice president in BCG's Boston office. For many years he led BCG's healthcare R&D business and now directs the global healthcare innovation and marketing agenda more broadly. Peter has served many leading pharmaceutical firms and has managed numerous assignments across all functions of the value chain. He has directed BCG's assessment of R&D productivity and is principal author of BCG's publications on the economics of R&D. Peter joined The Boston Consulting Group in 1989. Outside BCG Dr. Tollman co-founded and was managing director of a health care investment company, MPM Capital. He is a Governor of the Jerusalem Academy of Music and Dance at the Hebrew University. Peter received his Ph.D. in engineering from the University of Cape Town and his M.B.A. with distinction from Columbia Business School.

Peter A. Ubel, M.D., is professor of medicine and professor of psychology at the University of Michigan, a primary care physician at the Ann Arbor Veterans Affairs Medical Center, Associate Director of the Michigan Robert Wood Johnson Clinical Scholars Program, and Director of the Center for Behavioral and Decision Sciences in Medicine at the University of Michigan. His research explores controversial issues about the role of

values and preferences in health care decision making, from decisions at the bedside to policy decisions. He uses the tools of decision psychology and behavioral economics to explore topics like informed consent, shared decision making and health care rationing. He is currently Principal Investigator of 3 RO1s from the NIH. Dr. Ubel has won many research awards, including a Presidential Early Career Award for Scientists and Engineers from President Clinton in 2000. He has written over 100 scientific articles, and his research has been widely reported on in the popular media. He is author of *Pricing Life: Why It Is Time for Health Care Rationing* (MIT Press 2000), and *You're Stronger Than You Think: Tapping the Secrets of Emotionally Resilient People* (McGraw-Hill 2006).

Steven Woloshin, M.D., M.S., is a general internist at the White River Junction Veterans Administration in Vermont and a senior researcher in the VA Outcomes Group, and an associate professor of medicine and community and family medicine at Dartmouth Medical School. Dr. Woloshin's work (in collaboration with Lisa Schwartz) focuses on improving the communication of medical information to patients, physicians, journalists, and policymakers, and has appeared in leading medical journals. Their work has focused on creating and testing practical ways to overcome two important barriers to good communication: (1) many people (patients, providers, journalists) are limited in their ability to interpret medical data; and (2) exaggerated and incomplete health messages are common. To this end, they are developing and testing material to help people understand medical statistics and the benefits and harms of prescription drugs, teach several medicine in the media workshops for journalists and write an occasional series for the *Washington Post* entitled "Healthy Skepticism."