



## Characterizing Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products: Workshop in Brief

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# Characterizing Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products— Workshop in Brief

Efforts are under way within the drug development community to enhance the evaluation and communication of the benefits and risks associated with pharmaceutical products, aimed at increasing the predictability, transparency, and efficiency of pharmaceutical regulatory decision making. The U.S. Food and Drug Administration (FDA) is developing an enhanced structured approach to assessing the benefits and risks in drug regulatory decision making to better communicate this aspect of the human drug review process.<sup>1</sup> As FDA has indicated in its draft PDUFA V Implementation Plan (February 2013)<sup>2</sup> (the FDA PDUFA Plan), an extensive body of evidence informs regulatory decisions on the safety and efficacy of a proposed product, but in many cases, FDA must draw conclusions from imperfect data. The FDA PDUFA Plan notes that identifying and evaluating sources of uncertainty in a regulatory application is an important part of an FDA new drug application reviewers' work; however, drawing conclusions in the face of uncertainty can be a complex and challenging task. Effectively communicating regulatory decisions necessarily includes explanation of the impact of uncertainty on decision making. The FDA PDUFA Plan suggests that FDA's enhanced structured approach is intended to serve as a template for product reviews and a vehicle to explain the basis of regulatory decisions.

On February 12, 2014, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation (the Forum) held a public workshop as the first of a two-part series to advance the development of more systematic and structured approaches to characterize and communicate the sources of uncertainty in the assessment of benefits and risks, as well as their implications for pharmaceutical regulatory decisions. Workshop presentations and discussions were convened to explore the science of identifying and characterizing uncertainty in scientific evidence and approaches to translate uncertainties into decisions that reflect the values of stakeholders. A second workshop on May 12, 2014, will explore approaches to communicating about scientific uncertainties.

This brief summary of the workshop provides highlights from the presentations and discussions. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum or the IOM, and they should not be construed as reflecting any group consensus. The workshop was webcast live, and online participants were able to contribute to discussion through the hashtag #UncertaintyWorkshopIOM. The presentations, videos, and tweets are archived on the Forum website: <http://www.iom.edu/BenefitRisk1> (accessed April 2, 2014). A full summary of this two-part workshop series will be available in late 2014.

## Potential sources of uncertainty in drug benefit-risk evaluation

Uncertainty is “central to the evaluation of data” said Janet Woodcock, FDA Center for Drug Evaluation and Research (CDER) Director. Woodcock emphasized that despite the substantial preclinical, nonclinical, and clinical requirements

<sup>1</sup> For more information, see <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm> (accessed April 2, 2014).

<sup>2</sup> FDA (Food and Drug Administration). 2013. Structured approach to benefit-risk assessment in drug regulatory decision-making: Draft PDUFA V Implementation Plan—February 2013, Fiscal Years 2013–2017. [http://patientnetwork.fda.gov/sites/default/files/fda\\_benefit-risk\\_draft\\_plan\\_final\\_for\\_posting.pdf](http://patientnetwork.fda.gov/sites/default/files/fda_benefit-risk_draft_plan_final_for_posting.pdf) (accessed April 2, 2014).

## The Range of Sources of Uncertainty

Woodcock presented a list of a range of sources of scientific uncertainty that, she said, generally stem from underlying variability in human biology, factors associated with the chemistry of a drug, and the research process:

- **Human Variability.** Uncertainties can arise because clinical trials cannot provide full information about effectiveness or harm in more variable real-world populations.
- **Clinical Trials.** The nature of the clinical trial process itself can give rise to uncertainty, said Woodcock. For example, the time-limited aspect of clinical research means that a trial cannot measure the effect of chronic or lifetime use. Limits on the numbers of people assessed in a trial can undermine efforts to determine whether differences are real or are “noise.”
- **Unknowns.** It is not always known what to investigate and what could be an important “domain of harm” to study. The “unknown unknowns,” where researchers do not know what data are missing or are not studied, have historically led to some of the biggest safety controversies, according to Woodcock.

The workshop focused primarily on uncertainties arising from the research process and the “unknown unknowns” cited by Woodcock. Many well-known mechanisms to address “known unknowns”—including safety science research and regulatory policy tools for drug assessment and monitoring—were not treated in depth at the workshop.

undergirding an application for regulatory approval (and post-marketing requirements), it is not possible to know everything there is to know about a drug at the time at which FDA must make an approval decision. The presence and amount of uncertainty is to be expected. Public audiences often do not understand scientific uncertainty, and misunderstandings can be exacerbated when FDA finds a drug to be “safe and effective” and yet issues accompanying safety alerts, said Woodcock.

Tarek Hammad, Merck & Co., Inc., noted that the benefit and risk assessment is a complex decision-making process with inherent quantitative and qualitative dimensions, reflecting an interaction among multiple streams of evidence with many stakeholders, and thus that *context matters* in the drug evaluation process. Hammad outlined three distinct but interrelated categories of uncertainty that stem from the research process: clinical, statistical, and methodological. *Clinical uncertainty* arises by virtue of the use of randomized controlled trials (RCTs) as our primary approach to examine the effects of drugs. Limitations include reliance on volunteers as clinical trial participants,

## Statement of Task

An ad hoc planning committee will plan two 1-day public workshops that will address the need to advance the development of more systematic and structured approaches to characterize and communicate: (a) the sources of uncertainty in the assessment of benefits and risks, and (b) their implications on pharmaceutical regulatory decisions. Specifically, the workshop will explore potential analytical and communication approaches and identify key considerations on their development, evaluation, and incorporation into pharmaceutical benefit-risk assessment. Uncertainty in drug review and decision making can arise from many sources. This workshop will consider the entire drug development lifecycle, including pre-market drug review and post-market safety surveillance. Subject matter experts will be invited to participate in the workshop through presentations and discussions that will:

- Discuss the challenges in applying more systematic approaches to characterizing and communicating uncertainty in the assessment of a drug’s benefits and risks.
- Identify potential approaches to characterize uncertainty in pharmaceutical benefit-risk assessment, drawing from various scientific and regulatory disciplines and domains.
- Identify possible principles, best practices, and resources that can facilitate the development, evaluation, and incorporation of such approaches in regulatory decision making.
- Explore principles and approaches to facilitate the communication of uncertainty in benefit-risk assessment to stakeholders, including the public.

inclusion/exclusion criteria limiting real-world application, potential for off-label use after a drug is approved, adverse events with a long latent period, and numerous others. *Statistical uncertainty*, according to Hammad, arises because “the system is designed for drugs to pass a test, not really to quantify the risk or the benefits.” Whenever sampling techniques are used, by definition, some error—and thus uncertainty—will remain. *Methodological uncertainties* include, among other things, the fact that RCTs are designed to assess benefits and risks in pre-market settings, but observational studies are generally employed post-market. Hammad also described multiple operational challenges transcending these three dimensions, including, for example, that there is a lack of common discussion about a threshold of risk tolerance among different stakeholders—regulators, payers, health care providers, and patients. He further commented that it is important not to conflate the concepts of uncertainty of the *extent of the risk* with uncertainty about the *willingness of the patient to accept that risk*.

Sebastian Schneeweiss, Harvard Medical School, further discussed methodological uncertainties introduced by Hammad. Schneeweiss categorized sources for uncertainty as chance, bias, and representativeness. Chance and bias (e.g., confounding, time-related biases, surveillance bias, and misclassification) affect internal validity. Chance is addressed through calculation of 95 percent confidence intervals. Bias is addressed through various approaches such as negative control outcomes, emulating trial populations, bias modeling, and sensitivity analyses. Representativeness affects external validity and can be addressed in an RCT through evaluation of subgroups. Schneeweiss noted that in general, sources of uncertainty vary between RCTs and observational studies and also differentially affect the assessment of benefits and harms. RCTs are typically how we obtain information about benefit, while observational studies are typically how we obtain broad information about harm. He presented mechanisms to deploy a system of interlocking studies to help address these issues and more effectively quantify uncertainty.

John Ioannidis, Stanford Prevention Research Center (SPRC), Stanford University School of Medicine, presented results from approaches he has used to assess the internal and external validity of RCTs. When trials have design flaws, their effect sizes can be exaggerated. Ioannidis argued that to address external generalizability, a trial needs to be compared against other trials done in the same field on questions that are relevant. He also noted that the outcomes of interest are whether one drug is better than another (rather than placebo) and the relative uncertainty for one drug versus another.

## Reducing Uncertainty Through Maximizing the Value of the Evidence

Two presenters focused on the quality of evidence available for regulatory decisions: trial registration and participant retention.

Deborah Zarin of ClinicalTrials.gov, National Library of Medicine, and National Institutes of Health noted that wide public registration of clinical trials, including results and key protocol details, would support the best possible evidence-based decision making. However, she said, not all clinical trials are registered, and not all registered trials can be found. Trials are often registered under names other than those provided in a new drug application, causing these trials to be “invisible” to registry search engines. Publication presents a similar data vacuum for decision makers.

Suboptimal participant retention is a long-standing challenge that can contribute to uncertainty in reviewing clinical trial data, because losing participants during the conduct of a clinical trial skews results in unpredictable ways. Michaela Kiernan of SPRC at the Stanford School of Medicine presented one promising innovative retention approach that could help to optimize both high and non-differential retention of subgroups. An ongoing weight loss study at SPRC involves educating potential participants prior to randomization about research methods, trial design, control conditions, random assignments, and the impact of dropouts.

The FDA PDUFA Plan identifies the following two areas of uncertainty as warranting additional attention:

1. *The translation of pre-market clinical trial data to the post-market setting in which an approved drug is used in a much wider patient population.* Several individual workshop participants noted that formal mechanisms could help assess outcomes for heterogeneous subpopulations that will use the drug differently than patients in clinical trials.
2. *A new finding emerges in a post-market setting where the basis for the finding comes from sources of varying levels of rigor.* Some individual workshop participants raised questions about how to improve observational studies so that data arising from those studies can be effectively included in the benefit-risk assessment.

## Identifying and evaluating uncertainty

Workshop co-chair Baruch Fischhoff, Carnegie Mellon University Departments of Social and Decision Sciences and Engineering and Public Policy, noted that a core aim of the workshop was to discuss potential scientific bases and methods for taking uncertainty into account and making it “cognitively tractable” for regulatory decision making. Individual speakers addressed methodologies to characterize uncertainty and discussed how lessons about decision theory techniques applied in other domains, including the ascertainment of patient and other stakeholder preferences, could help inform pharmaceutical regulatory decision making.

## Synthesizing uncertainties into comprehensible representations

Expert elicitation techniques and Bayesian statistical methods, two innovative methods to characterize and account for uncertainty, could help inform the development of new approaches to characterizing and representing uncertainty in the regulatory domain. These two methods provide a scientific basis for “using judgment to supplement standard statistical tests,” noted a workshop participant.

### Decisions Made Under Uncertainty: Tysabri and Anoro Ellipta Case Studies

Patrick Frey, FDA CDER, provided an overview of FDA’s approach to evaluating benefits and risks of pharmaceutical products, with specific focus on how these approaches take sources of uncertainty into consideration. The FDA PDUFA Plan notes that systematic approaches to evaluating uncertainty is an area worthy of further consideration to inform the drawing of conclusions in the context of uncertainty. Frey stated that FDA is interested in exploring a systematic approach to uncertainty, much like the benefit-risk framework. FDA developed two case studies to illustrate the types of complex uncertainties that FDA reviewers must address when making decisions based on clinical evidence. These case studies were prepared and presented to describe real-life examples of uncertainty that a regulator faces to illuminate evaluation of uncertainty in assessment of the benefits and risks through the eyes of a regulator. The case studies can be accessed at the meeting website and will be further discussed at the second workshop.<sup>a</sup>

**Tysabri (natalizumab).** Robert Temple, FDA CDER, described the Tysabri case study. Four months after its initial approval to treat patients with multiple sclerosis (MS), Tysabri (natalizumab) was withdrawn from the market because two patients died after developing a life-threatening, often fatal, brain infection called progressive multifocal leukoencephalopathy (PML). At the time, there was considerable uncertainty about the magnitude of the risk of PML to patients exposed to Tysabri and whether there were any identifiable risk factors that could reliably identify patients at greater risk. In determining whether to allow re-marketing of the drug, FDA considered whether the risk of PML (and uncertainty about the risk) outweighed the drug’s recognized substantial benefit. The agency examined additional data provided by the company developing the drug and consulted with an advisory committee that included patients with MS. Temple noted that while patients plainly understood the risk that contracting PML could be fatal, they provided “powerful personal testimony” in favor of reintroducing Tysabri. In response, FDA allowed marketing of Tysabri to resume, accompanied by an extensive risk mitigation plan that included requirements for strict labeling and safety information; controlled distribution; and a prospective, observational post-marketing study, following at least 5,000 patients for 5 years.

**Anoro Ellipta.** The case study on Anoro Ellipta (umeclidinium and vilanterol inhalation powder) was outlined by Jennifer Rodriguez Pippins, a clinical reviewer in FDA CDER. In December 2013, FDA approved Anoro Ellipta as a long-term maintenance treatment for patients with chronic obstructive pulmonary disease. One of its agents, umeclidinium, is a member of a class of long-acting agents that have been the subject of concern since 2007, when pooled analyses suggested increased cardiovascular (CV) risks associated with another drug in the same class. The low numbers of major cardiac events in Anoro Ellipta’s premarket clinical trials made it difficult to draw definitive conclusions about CV risk. According to Pippins, FDA’s view was that the observational studies the sponsor proposed would not be able to provide a definitive assessment of cardiac risk; as a result, the agency decided not to require post-market monitoring.

<sup>a</sup> See <http://www.iom.edu/BenefitRisk1> (accessed April 2, 2014).

**Expert elicitation** involves the process of seeking carefully reasoned judgments from experts about an uncertain quantity or process, often in the form of subjective probability distributions, according to M. Granger Morgan, Carnegie Mellon University Department of Engineering and Public Policy. A key benefit offered by expert elicitation is that informal evidence informing the expert’s judgment can be incorporated alongside formal evidence, said Morgan. Expert elicitation can be applied to uncertainty not only about a quantity but also about a process or model functional form, such as the relative likelihood that alternative models of possible pharmacokinetic and pharmacodynamics processes correctly describe a given biological process. With respect to any application of expert elicitation, Morgan cautioned that: (1) people who have predictive expertise must be available to address the topic; (2) qualitative uncertainty words such as “likely” and “unlikely” can mean very different things to different people or to the same people in different situations; and (3) expert judgments can be limited by certain cognitive heuristics, including “availability” and “anchoring and adjustment.”

*Availability.* Morgan noted that people assess the frequency of a class, or the probability of an event, by the ease with which instances or occurrences can be brought to mind. Safeguards and other graphical aids can be used to ensure that experts have the full complement of information in mind when answering questions.

*Anchoring and Adjustment.* If people start with a first value (“anchor”) and then adjust up and down from that value, they typically do not adjust sufficiently. It is best not to begin an elicitation with a question about what is the “best” or “most probable” value but rather to begin work by establishing outer ranges and then move in toward estimates of best value, said Morgan.

**Bayesian approaches**, described by Joel Greenhouse, Carnegie Mellon University Department of Statistics, can permit the introduction of judgments about plausible values within a given study to affect the summary of the belief about the treatment effect being studied. These judgments, or “likelihood,” are emerging information about an ongoing trial. Greenhouse described how the summary of the treatment effect prior to a trial, or “prior distribution,” can also be adjusted to take into account judgments about whether particular information ought to be discounted; for example, previous studies that are thought to be relevant but not directly related might be “down weighted” in this manner, which has the effect of reducing the sample size of that relevant prior information. The prior distribution and the likelihood are ways to formalize and make transparent assumptions by representing uncertainties in terms of probability distributions. Applying Bayes rule and Bayesian methodology, these mechanisms can be used to produce information, called the “posterior distribution,” that can summarize the belief about the treatment effect. Greenhouse added that sensitivity analysis can be used to test how assumptions about the prior distribution affect the posterior inference. He noted that “[i]f it does not change very much, that gives you added confidence that the conclusions are not being driven by the prior [distribution]. If it does change a lot, that ... tells you how much uncertainty you have ... in the available evidence about the question of interest.”

## Applying decision theory approaches to regulatory decision making

Several speaker presentations generally addressed decision theory *techniques* and the *scientific basis for incorporating patient and other stakeholder preferences*. Several speakers suggested that scientific methodologies for the incorporation of expert deliberation and stakeholder perspectives can help to improve certainty of forecasts, place what is known and what is unknown in a practical context, address uncertainties in the context of patient preferences, reveal new uncertainties that otherwise may have been overlooked, and provide important information on values for regulatory determinations.

Decision theory *techniques* that could be applied in the context of regulatory decision making include the application of standards to the characterization of uncertainty. David Mandel, Toronto Research Centre Department of Defense Research and Development Canada, provided lessons from the domain of intelligence assessments, noting that “most finished intelligence is ... human judgment and not simply the communication of something factual.” It follows that it is important to be clear about what is certain knowledge versus what is the product of reasoned judgment.

Mandel reinforced Morgan's comments that qualitative uncertainty words are severely limited in their ability to convey accurate information, noting that "words are imprecise and vague, their imprecision varies across individuals, and is not necessarily aligned with normative meanings." Mandel suggested the adoption of correctional measures, including omitting "weasel words" (such as "reportedly" and "indicates") and institutionalizing a rank ordering of terms using specific and common guidelines. The use of numbers to quantify and communicate uncertainty carries the advantage of precision, allowing operations (such as multiplication of probabilities or other ways to measure the conjunction of events), and verification of the discrimination and calibration skill of analysts.

Several speakers addressed the *scientific basis for incorporating patient and other stakeholder preferences*. Joe Arvai, University of Calgary Department of Geography, described ways to characterize and account for the "social context for respectful, effective elicitation" of stakeholder preferences. As a foundational matter, he said, preferences or judgments are "constructed" and not simply "uncovered," based on cues present during the decision-making process. These constructive processes especially occur when the decision problem is context or novel; quantitative-qualitative translation is necessary; or tradeoffs must be made. Arvai presented a scientific framework for structured decision making following six steps: (1) define problems, opportunities, and constraints and identify stakeholders; (2) identify objectives and appropriate performance measures; (3) develop sensible, creative, and substantially different alternatives; (4) forecast consequences and uncertainties and identify thresholds and tipping points; (5) confront tradeoffs explicitly and thoroughly; and (6) implement decisions and monitor, learn, and adapt. Arvai suggested that sensitivity analysis can be used to account for uncertainty by looking at point estimates within ranges and making tradeoffs at various range levels to ascertain how sensitive the constructed preferences are to different levels of uncertainty. He added that composite indices can be created to assess uncertainty across a suite of attributes rather than through point-by-point sensitivity analysis. In this process, tolerance for uncertainty can itself be treated as its own objective to be included in the assessment of alternatives.

Timothy McDaniels, University of British Columbia Institute of Resources and Environment, emphasized that eliciting values for risk management choices involves the application of structured (rather than informal) common sense to complex problems. McDaniels offered several principles and themes of eliciting values for risk decisions, noting:

- Eliciting values for risk choices entails the combination of technical and scientific information about the performance of alternatives on one hand, and value-based preferences or judgments on the other, to clarify and examine tradeoffs. McDaniels emphasized that this process should be explicit and transparent.
- The acceptable level of risk within a decision context should be a function of the available alternatives and not just a single threshold to allow full consideration of the tradeoffs involved in the risk decision.
- Multiple conflicting objectives are best addressed by keeping the dimensions and valuation judgments separate, in natural units.
- When faced with deep uncertainties, learning over time and flexibility to adapt are key components of the process and will promote the consideration of robust and resilient alternatives that could work better over a wide range of uncertainties.
- Decisions must be made before all uncertainties are resolved; "surprises" are a potential part of any risk decision process.

Individual workshop participants noted a number of FDA attributes and processes that currently incorporate, or could be enhanced to incorporate, the scientific methods and approaches discussed to enhance decision making under or with respect to uncertainty.

- *FDA structure, authorities, and processes*. McDaniels commented that FDA has clear authorities conferred upon it by statute, with transparent processes allowing for an environment in which informed choices can be made among alternatives within a structured framework. He further noted that FDA has adopted an approach for eliciting stakeholder values through the consultative process the agency is employing in developing its benefit-risk framework.

- *Expert elicitation.* Several workshop participants, including Lisa LaVange, FDA CDER Office of Biostatistics, noted that FDA has established processes and mechanisms for engaging experts in regulatory decision making, most notably through the convening of advisory committees. McDaniels noted that the advisory panel structure could potentially be further enhanced through a structured or formal attention to stakeholder values elicited through that process.
- *Bayesian statistical methods.* Formal Bayesian methods have not been adopted generally by FDA for the evaluation of pharmaceuticals. According to LaVange, however, there are several possible applications for Bayesian methods to be considered, including safety studies, where evidence accumulates over time; non-inferiority trials, because they call for the incorporation of historical data of comparator drug(s); and antibiotics development, in part because the mechanism of action is more evident: “I can look at a dish of bugs and see if a drug kills them.”
- *Risk management strategies, including the Risk Evaluation and Mitigation Strategy (REMS) mechanism.* Several workshop participants, including Theresa Mullin, FDA CDER Office of Strategic Programs, noted that the Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a REMS in connection with approval of a marketing application (or later if new safety information emerges). FDA may require a REMS if it determines such action necessary to ensure that the benefits of a drug or biological product outweigh its risks. As outlined in FDA’s Draft REMS Guidance for Industry,<sup>3</sup> REMS could include, as required by FDA, a special medication guide or patient package insert; a communication plan targeted to health care providers; and elements to ensure safe use, including training, certification, or other monitoring. McDaniels commented that to the extent that the REMS structure provides more approval alternatives (other than approve without conditions/disapprove) and includes ability to learn over time from monitoring, such a system constitutes a very valuable tool for applying risk-management choices in a structured format.
- *Proposed new regulatory pathways.* Although the focus of the workshop was on consideration of scientific methods that could be applied to the existing regulatory authorities and processes currently available to FDA, there was some discussion among individual workshop participants about regulatory approval pathways that do not currently exist but have been proposed that could address certain aspects of the uncertainty issues. For example, a workshop participant noted that the Special Medical Use (SMU) pathway was proposed in part to take into account that certain severely affected subpopulations that do not have many treatment options might be willing to accept greater uncertainty and greater risk. The SMU regulatory mechanism would limit use of products approved under that pathway to specified populations while requiring additional evidence development and safety surveillance in the post-market setting. Charles Manski, Northwestern University Department of Economics, presented a proposal for broadened approval options under a system of “adaptive partial approval,” similar in concept to “adaptive licensing” proposals made by others in the field. The adaptive approval mechanism suggested by Manski would allow for earlier approval of a broader class of products than those contemplated in the SMU proposal, coupled with limited use and further evidence-gathering requirements. Many individual workshop participants noted limitations and concerns associated with an adaptive approval approach, most notably that retention of participants in ongoing clinical trials could be significantly undermined by the availability on the market, even on a limited basis, of the product being studied. 

<sup>3</sup> FDA. 2009. Guidance for industry: Format and content of proposed Risk Evaluation and Mitigation Strategies (REMS), REMS assessments, and proposed REMS modifications—Draft guidance (September 2009). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> (accessed April 2, 2014).

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\*\*IOM planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The statements made are those of the authors or individual meeting participants and do not necessarily represent the views of all meeting participants, the planning committee, or the National Academies.

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For additional information regarding the meeting, visit [www.iom.edu/BenefitRisk1](http://www.iom.edu/BenefitRisk1).

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