Advancing Structured Benefit-Risk Assessment in FDA Review

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Discussion Guide

In order for a drug to be approved, it must be deemed safe and effective for its intended use based on evidence from adequate and well-controlled studies. The FDA has interpreted "safe and effective" to mean that the benefits outweigh the risks. Reviewers, however, must make this determination based on a tremendous amount of complex data, and must do so in contexts where there is a great deal of uncertainty. This uncertainty can stem from a variety of sources, including the nature of a given drug's benefits and risks, its effectiveness in a real-world population, and its long-term safety. For example, pre-market data are derived from randomized control trials (RCTs), which assess the efficacy of a drug in a highly controlled, narrow population that may not be representative of the wider population that may ultimately use the drug.[1] New information about potential harms or adverse events is gathered post-market, but there is uncertainty over how to reconcile results from observational studies with those from clinical trials.[2]

In order to increase the predictability, transparency, and efficiency of its decision-making process, FDA developed and piloted a structured framework for benefit-risk assessment starting in 2012. This framework is designed to help characterize and communicate uncertainties, and to reflect the iterative nature of the benefit-risk assessment process at FDA, where new findings can be incorporated into the framework as more information becomes available in the post-market setting.[3] With the qualitative framework now in place, many stakeholders have expressed interest in the use of more quantitative approaches to benefit-risk assessment. As part of its next steps in refining this framework, the agency is exploring how these more technical and decision-analytic approaches may enhance the value of the framework and support FDA decision-making.

To support progress in this area, and, the Duke-Margolis Center for Health Policy is convening this expert workshop under a cooperative agreement with FDA to discuss: 1) when and how application of structured benefit-risk assessment approaches and tools can contribute the greatest value to support regulatory decision-making, 2) key considerations for ensuring that benefit-risk assessment approaches and tools are fit-for-purpose in FDA's drug regulatory context, and 3) strategies for incorporating patient input (derived through both qualitative and quantitative methods) into structured benefit-risk assessment.

FDA Efforts to Advance Structured Benefit-Risk Assessment

FDA began exploring more systematic approaches to benefit-risk assessment in 2009 as part of a broader effort to improve the clarity, transparency, and consistency of the agency's decision-making process.[4] The goal was to develop a qualitative, descriptive framework that could act as a template for product reviews and clearly communicate the reasoning behind approval decisions.[5] Between 2009 and 2011, the agency developed an initial structure for the Benefit-Risk Framework, which was subsequently piloted within review divisions beginning in 2012.[6] It has since been refined and integrated within the decision-making processes of both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). FDA's work in this area paralleled similar efforts by industry and other regulatory agencies, such as the European Medicines Agency (EMA), to develop

structured formal benefit-risk frameworks. (See the next section for an overview of FDA's Benefit-Risk Framework).

Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)
Enhancing FDA's benefit-risk decision-making process was also a key topic during negotiations for the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which was approved in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). As part of its commitments under that legislation, the agency published a five-year plan to further develop and implement the structured Benefit-Risk Framework within the drug review process, train reviewers and decision-makers in its use, and refine it over time.[7]

FDA also committed to hold two public workshops on benefit-risk assessment. FDA held the first public workshop in 2014,[8] in partnership with the Institute of Medicine (IOM). This meeting brought together key experts in decision and regulatory sciences to identify and discuss potential approaches to evaluating the uncertainty inherent in complex review decisions, including consideration of more technical, quantitative approaches such as expert elicitation methods and Bayesian statistical methods. A formal summary of the workshop discussion, *Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products,* was published in September 2014.[9]

FDA held its second meeting in September 2017, focused on the experiences and key learnings of FDA, other regulators, pharmaceutical industry, and patient stakeholders on benefit-risk assessment. Topics of this meeting included: regulatory and industry experiences with implementing structured benefit-risk approaches; approaches to incorporating patient perspectives into structured benefit-risk assessment; exploration of methods to advance structured benefit-risk assessment; and communicating benefit-risk assessment to the public. The meeting webcast and slides are available on the FDA meeting page: https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm378861.htm

The FDA also committed to creating the Patient-Focused Drug Development (PFDD) Initiative, which aims to gather direct patient input on several specific diseases.[10,11] The goal of this effort is to provide the agency with a more systematic approach to elicit the patient perspective, particularly regarding the impact of the disease on their lives as well as the treatment options available to them. To date, the FDA has held 24 PFDD meetings. The input from these meetings is summarized in disease-specific *Voice of the Patient* reports that are intended to provide critical context for both FDA reviewers and other stakeholders.[12]

21st Century Cures Act
The 21st Century Cures Act of 2016 further emphasizes the role of patient input. The Act requires the FDA to develop guidance documents on the collection of "patient experience data" and its use in drug development. These data include information regarding patients' experiences with a disease, the impact of the disease on patients' lives, and patient preferences with respect to treatment for that disease.[13] One of these guidance documents will specifically address how FDA anticipates using relevant patient experience data in relation to the structured Benefit-Risk Framework for regulatory decision-making.[14] These requirements represent a next step in the agency's broader efforts to enhance benefit-risk assessment and ensure that it is more patient-centered.

Food and Drug Reauthorization Act of 2017 (FDARA)
The agency's next steps in refining the Benefit-Risk Framework will be guided by commitments outlined in PDUFA VI, which was included in the Food and Drug Reauthorization Act of 2017 (FDARA).[15] Under

these commitments, FDA will update its implementation plan for the Benefit-Risk Framework. This will include a report on the progress made under PDUFA V and a plan for continued implementation over the next five years.[16] FDA must also publish draft guidance on benefit-risk assessment, including how the framework can be applied throughout a drug's lifecycle and how to communicate FDA's approach to benefit-risk assessment to the public.

The agency will also develop a series of guidance documents on approaches for translating PFDD meetings into fit-for-purpose tools that can be used to collect meaningful patient and caregiver input.[17] These approaches will be a key component in advancing the inclusion of the patient perspective into the FDA's benefit-risk assessment process.

ICH Guidelines on Benefits and Risks

Guidance on communicating benefit-risk decisions is also available from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which published revisions to its guidance document *M4E: The CTD – Efficacy* in 2016. The updated document includes new recommendations for formatting and structuring benefit-risk assessments to better communicate to regulators the thought process behind sponsor benefit-risk decisions (i.e., section 2.5.6).[18,19] Importantly, this section does not offer a prescribed approach to benefit-risk assessment, but allows applicants the flexibility to apply different benefit-risk approaches.[20]

Overview of the Structured Benefit-Risk Framework

The Benefit-Risk Framework serves as a standalone, succinct explanation of the most important aspects of the regulatory recommendation or decision and the factors that carried the greatest weight in those conclusions. The Benefit-Risk Framework (Figure 1) has two main elements: the Benefit-Risk Dimensions and the Benefit-Risk Integrated Assessment. The Benefit-Risk Framework includes five key dimensions: *Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management*.[21] The Benefit-Risk Framework is accompanied by guiding questions, and reviewers receive training and written guidance to facilitate completion of the Benefit-Risk Frameworks in a consistent manner.

Figure 1: FDA Benefit-Risk Framework for Human Drug Review

Benefit-Risk Integrated Assessment		

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		

The first two dimensions, *Analysis of Condition* and *Current Treatment Options*, assess the needs of the patient population, including aspects of the condition that are not well-addressed by available therapies. This assessment represents the Benefit-Risk Framework's therapeutic context, which provides useful information for weighing the benefits and risks of the drug under review. This discussion is not specific to the particular product under review.

The *Benefit, Risk,* and *Risk Management* rows relate specifically to the drug under review. *Benefit* focuses on the drug's purported benefits to patients, such as the strengths and limitations of the clinical trials, the clinical relevance of the endpoints, the magnitude and durability of the effect(s), any notable variability in efficacy across subpopulations, generalizability of effectiveness to anticipated real-world use, and any important missing information. *Risk* discusses important considerations on safety, such as the adequacy of the safety database, likelihood and severity of adverse events, and considerations of use in the post-market setting. *Risk Management* includes efforts that could help manage or further characterize the identified safety concerns, such as boxed warnings or other labeling recommendations, post-marketing requirements or commitments (PMRs/PMCs) or a Risk Evaluation and Mitigation Strategy (REMS).

The Benefit-Risk Framework columns delineate the two types of information considered for each of these dimensions. *Evidence and Uncertainties* summarizes the supporting information most relevant to the regulatory decision such as key facts, study findings, and uncertainties that stem from study limitations and data gaps. *Conclusions and Reasons* presents the interpretation of the *Evidence and Uncertainties* and any potential implications upon the regulatory decision.

The *Benefit-Risk Integrated Assessment* (appearing at the top of the Benefit-Risk Framework) is a summary of the final regulatory decision. It explains the reasoning behind the decision and any critical clinical judgments that contributed to the decision. The summary integrates the analysis of the product's benefits and risks and explains how evidence and uncertainties helped the agency reach the conclusion. The summary also explains the rationale for labeling and risk management decisions as well as for any post-marketing requirements. Where applicable, it may capture differences in opinions within the review team and explain how those differences were resolved.

The structured Benefit-Risk Assessment Framework is now a foundational component of regulatory decision-making for CDER and CBER. Complete Benefit-Risk Frameworks now appear in the publicly available review documents for approved novel drugs, and can be accessed at drugs@fda,[22] searching for the drug's name. Examples, include Spinraza (nusinersin),[23] Rubraca (recaparib),[24] and Adlyxin (lixisenatide).[25]

Further development and refinement of the framework is ongoing, and many stakeholders are interested in exploring more technical or quantitative approaches to benefit-risk assessment. Such methods may help to describe the uncertainty that is inherent in complex review decisions and support sensitivity analyses to explore the impact that uncertainty may have on the regulatory decision. In some cases, approaches may include techniques to make more explicit how the tradeoffs between benefits and risks are assessed. However, there are questions over when and how these approaches can provide the greatest value in supporting FDA's decision-making and how to ensure these approaches are fit-for-purpose.

Decision-Analytic Approaches for Benefit-Risk Assessment

A broad range of approaches have been developed to support systematic and evidence-based benefit-risk assessment. These approaches include both overarching frameworks that can be used to guide complex decision-making processes and specific tools and methods that can be applied to particular decisions (See the Suggested Reading List in Appendix I for additional reading on selected methods and approaches). These frameworks may incorporate a range of qualitative or quantitative approaches. The *FDA's Benefit-Risk Framework*, for example, is on the qualitative and descriptive end of the spectrum, while the *Unified Methodologies for Benefit-Risk Assessment (UMBRA)* framework is an example of a mixed-methods approach that incorporates some quantitative elements within its defined steps.[26,27] The *Multi-Criteria Decision Analysis (MCDA)* framework is on the more quantitative end of the spectrum. MCDA enables decision-makers to quantify the tradeoffs associated with a drug and its comparators by scoring and weighting multiple benefit and risk criteria.[28]

The **PROTECT** (**P**harmacoepidemiological **R**esearch on **O**utcomes of **T**herapeutics by a **E**uropean **C**onsortium) Benefit-Risk group has identified and summarized more than 45 approaches across this spectrum that can be applied to benefit-risk assessment.[29] While this list is not exhaustive, the approaches highlighted in this resource underscore the range of tools that are available to stakeholders. Each relies on different data, has unique characteristics and features, and offers different strengths and limitations.

The use of more technical or quantitative benefit-risk approaches as part of FDA decision-making has been widely discussed, including during the 2014 IOM workshop on benefit-risk assessment. This workshop highlighted two approaches in particular: expert elicitation and Bayesian approaches. Expert elicitation is a technique that uses surveys to formally gain input on topics where there is uncertainty about the available data.[30] The elicitation process includes obtaining a series of experts' views to demonstrate the range of opinions related to the area of uncertainty. These views are often quantified into the form of subjective probability distributions, which can be a valuable addition to the current available evidence.[31] Bayesian approaches and other probabilistic models have also been proposed to address uncertainty. Bayesian methods incorporate existing information from earlier phase trials or natural history studies to build prior probability distributions into the analysis. These prior distributions are then updated with observed data from the trial to generate posterior probabilities about the treatment effects. These methods can formalize and make transparent the assumptions that are made in conditions of uncertainty.[32] However, there are a range of other methods or approaches that may be relevant to FDA decision-making, including value trees, influence diagrams, effects tables, probabilistic quantitative computer simulations, and a variety of visualization tools.

Additionally, there are a range of quantitative and qualitative methods that may be applied to understand patients' priorities, preferences, and information needs. An example of a qualitative approach is FDA's Patient-Focused Drug Development initiative and the resulting *Voice of the Patient* reports, which have been viewed as an effective means to gather input from an engaged set patients and their caregivers. An example of a quantitative approach includes formalized stated-preference methods, such as discrete choice experiments and best-worst scaling,[33] to obtain systematic evidence quantifying the relative importance of specific benefit and risk attributes that may characterize an actual or potential therapy. Both qualitative and quantitative methods appear to be gaining traction in the drug development space. However, there are several outstanding questions over how to appropriately apply any these methods in the drug regulatory context, including how best to adapt existing methods to make them fit-for-purpose, as well as how to interpret and apply the findings within formal drug review processes.

Meeting Objectives

The purpose of this workshop is to explore the potential for quantitative and decision-analytic approaches to support the FDA review process for certain complex submissions. The current structured benefit-risk assessment approach will continue to be the foundation of FDA review process. Discussion will encompass several technical decision-analytic approaches and case study vignettes. We will also discuss how patient preferences and perspectives might be incorporated into structured benefit-risk approaches. Input from this meeting will support the FDA in its continued efforts to advance structured benefit-risk assessment in FDA's human drug review process.

Session I: Defining the Potential for Decision-Analytic Approaches to Inform the Benefit-Risk Framework

Objective: Discuss the value of the Benefit-Risk Framework as a structured qualitative approach and explore opportunities for strengthening and clarifying the role and value of the framework. Discussion will elicit perspectives on, broadly, how targeted application of more technical approaches within the framework may add value to regulatory benefit-risk assessment. Discussion will also identify important regulatory constraints and parameters that impact the feasibility and applicability of these approaches.

Questions to address:
- What are possible opportunities for strengthening the value of the Benefit-Risk Framework? (e.g., making the Benefit-Risk Framework a standard communication tool, integrating it into Advisory Committee Meetings, etc.)
- What additional value could more formal decision-analytic approaches bring to FDA's benefit-risk assessment process, and in what situations?
- What are the important questions that need to be addressed in order to successfully apply such approaches in the context of drug regulatory evaluation (i.e., to ensure they are fit-for-purpose)?

Session II: Framing Decision Problems and Characterizing Uncertainties about Benefits and Risks

Objective: Explore more structured methods (beyond the current framework) to frame complex regulatory decision problems and characterize uncertainty about the benefits and risks of a drug. Types of approaches (qualitative, semi-quantitative, and quantitative) that may be relevant to this topic include decision trees, value trees, visualization tools, subjective probability elicitation, and probabilistic modeling.

Questions to address:
- In what situations (e.g. types of regulatory decisions) could the approaches described above add value to the benefit-risk assessment and communication, and how?
- How could such approaches be integrated into drug review and the Benefit-Risk Framework, from a process point of view?
    - What would be required from FDA review staff?
    - Are there processes to engage external experts?
    - What information would be needed from the Applicant?
- What are the key considerations for ensuring these approaches are fit-for-purpose within those contexts? (i.e., sufficiently transparent to all stakeholders, adequately supports clear judgment, etc.)
- What might be realistic measures of success in applying these approaches?

Session III: Weighing Benefits and Risks in Human Drug Review

Objective: Examine qualitative and quantitative decision-analysis methods that can be used to support FDA efforts to make tradeoffs about the benefits and the risks (including uncertainties) of a given product. Types of methods that may be relevant to this topic include weighting processes and sensitivity analyses of various kinds.

Questions to address:
- Understanding that these types of approaches may require significant effort, in what situations should FDA consider applying more formal processes to assessing benefits *versus* risks approaches to support their decision-making?
    - Are there specific approaches that may be most tractable in certain circumstances?
- How could such approaches be integrated into both drug review and the Benefit-Risk Framework, from a process point of view?
    - What would be required from FDA review staff?
    - Are there processes to engage external experts?
    - What information would be needed from the Applicant?
- What are the key considerations for ensuring these approaches are fit-for-purpose within those contexts? (i.e., sufficiently transparent to all stakeholders, adequately supports clear judgment, etc.) What might be realistic measures of success in applying these approaches?

Session IV: Incorporating Patient Input into Benefit-Risk Assessment

Objective: Explore outstanding questions regarding formally applying and using systematic approaches to assessing patients' priorities, preferences, and information needs to inform FDA's benefit-risk assessments. Approaches may include formal methods such as discrete choice analysis or best-worst scaling, but it must be recognized that patient input can come from many other sources. A goal of this session is to outline concrete steps that can be undertaken in order to address methodological and practical challenges with applying such methods in the drug regulatory context.

Questions to address:
- In what situations could dedicated patient preference studies add the most value to CDER's and CBER's benefit-risk assessments, and how?
- What are the key regulatory considerations for ensuring that these approaches can support CDER's and CBER's benefit-risk assessments?
- In lieu of patient preference studies, are there other approaches that FDA could consider to more systematically incorporate patient input into benefit-risk assessment?

Session V: Identifying Key Themes and Potential Paths Forward

Objective: Reflect on the day's discussion, specifically revisiting any key concerns or issues that were identified in Session I, as well as any themes that emerged throughout the day.

Questions to address:
- What are the key considerations for FDA as it continues its efforts to incorporate more decision-analytic approaches into drug review?
- What is a research agenda that would help advance the use of these methods to support FDA decision-making?

Appendix I: Suggested Reading List

Colopy, M., Damaraju, C. V., et al. (2015). Benefit-Risk Evaluation and Decision Making: Some Practical Insights. *Therapeutic Innovation & Regulatory Science*. Retrieved from http://journals.sagepub.com/doi/pdf/10.1177/2168479014565469

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