Duke | Robert J. Margolis, MD Center for Health Policy

Advancing Structured Benefit-Risk Assessment in FDA Review

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Meeting Summary

Background

In order for a drug or biologic to be approved for marketing, it must be deemed safe and effective for its intended use – in other words, its benefits must outweigh its risks. FDA's 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 about the product's potential benefits and harms to the patients who may use the product in the real-world setting. To increase the consistency, transparency, and clarity of its decision-making process, FDA developed and implemented a qualitative, structured framework for benefit-risk assessment. This framework is designed to help characterize and communicate uncertainties, and to reflect the dynamic and iterative nature of the benefit-risk assessment process at FDA.[1] With the qualitative framework now in place, many stakeholders have expressed interest in the use of more quantitative and decision-analytic approaches to benefit-risk assessment. 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.

Development and Implementation of the Structured Benefit-Risk Framework

FDA began exploring more systematic approaches to benefit-risk assessment in 2009.[2] The goal was to develop a framework that could act as a template for complex product reviews and clearly communicate the reasoning behind approval decisions.[3] In developing the Benefit-Risk Framework, the agency examined both quantitative and qualitative approaches to benefit-risk assessment, and concluded that a qualitative overarching framework was the best vehicle to rigorously communicate the key benefit-risk considerations, while being flexible enough to accommodate quantitative supporting information.

The Benefit-Risk Framework serves as a succinct explanation of the most important aspects of a regulatory 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 four dimensions[4]: *Analysis of Condition, Current Treatment Options, Benefit, and Risk and Risk Management*.[5] These four dimensions are the key decision factors that are the basis of any decision. The *Benefit-Risk Integrated Assessment* is a summary of the final regulatory decision. It explains the reasoning behind the decision, integrates the analysis of the product's benefits and risks, and explains how evidence and uncertainties helped reach the conclusion.

As part of the 2012 re-authorization of the Prescription Drug User Fee Act (PDUFA V), FDA committed to publishing 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.[6] The Benefit-Risk Framework is now a foundational component of regulatory decision-making for the

Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

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 and Risk Management		

The agency's next steps in refining the Benefit-Risk Framework will be guided in part by commitments outlined in PDUFA VI, which were passed as part of the Food and Drug Reauthorization Act of 2017 (FDARA).[7] Under these new commitments, FDA will update its implementation plan for the Benefit-Risk Framework and 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.

Opportunities to Further Advance Structured Benefit-Risk Assessment

With further development and refinement of the framework ongoing, many stakeholders are interested in exploring more quantitative or decision-analytic approaches to benefit-risk assessment. A range of both qualitative and quantitative approaches have been developed to support systematic and evidence-based benefit-risk assessment, and which may help to describe the uncertainty that is inherent in complex review decisions or make more explicit how the tradeoffs between benefits and risks are assessed.

Stakeholders have also expressed interest in how to more effectively incorporate the patient perspective into benefit-risk assessment. These efforts align with commitments under PDUFA V, PDUFA VI, as well as requirements set forth in the 21st Century Cures Act, which all include elements addressing how patient input can better inform drug development and regulatory decision-making. Here, too, there are a number of quantitative and qualitative methods that may be applied to understand patients' priorities and preferences, and these methods appear to be gaining traction in the drug development space. However, there are several outstanding questions over how to appropriately apply any of 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

In light of these ongoing questions, and under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Duke-Margolis Center for Health Policy convened an expert workshop on October 4, 2017 entitled, "Advancing Structured Benefit-Risk Assessment in FDA Review" to explore the potential for quantitative and decision-analytic approaches to support the FDA review process for certain complex submissions. The objectives of the workshop were 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.

This workshop provided an opportunity for representatives from across academia, industry, and government to explore and discuss how to strengthen the value of the Benefit-Risk Framework through the application of technical and decision-analytic approaches to structured benefit-risk assessment in both the pre-market and post-market review of drugs and biologics. Discussion encompassed several technical decision-analytic approaches and case study vignettes, as well as how patient preferences might be incorporated into structured benefit-risk approaches. The following text represents a summary of the meeting and showcases a range of participant perspectives, though it does not necessarily reflect a consensus among the group.

Strengthening the Value and Role of the Benefit-Risk Framework

Discussion first focused on the successes of the Benefit-Risk Framework to date, as well as opportunities to strengthen the value of the Framework more generally. The Benefit-Risk Framework was created with a number of a goals in mind: 1) to provide a clear snapshot of a particular regulatory decision, 2) to articulate the applied clinical reasoning and judgment to a decision, 3) to improve transparency in the decision-making process, and 4) to provide an accessible record of the decision. Participants noted that the Benefit-Risk Framework is effective in communicating the reasoning behind regulatory decisions, and agreed that it was useful, clear, and understandable to a range of stakeholder groups including FDA, applicants, patients, and healthcare providers.

Though the Benefit-Risk Framework has primarily served as a communication tool, it was generally agreed that there is substantial scope to enhance use of the Framework as a decision-making tool. Rather than filling out the sections of the Framework near the end of the review process, reviewers should utilize the Framework throughout the decision-making process to help guide and clarify their thinking. However, some participants noted that there will continue to need to be outreach to teach reviewers to use the Framework in this way.

Some participants also requested more clarity on how the Framework can be used throughout the lifecycle of a drug, particularly in the Investigational New Drug (IND) stage during discussions between FDA and sponsors, and in the post-market setting when new information about a drug's benefits or risks becomes available. Others recommended that FDA revisit previous benefit-risk decisions—including decisions where the drug was ultimately not approved—to identify contexts where the Framework was useful and where it could be improved.

Participants also recommended adding new elements that could advance the existing Framework. Including data summaries and visualizations as part of the final decision, for example, could provide greater transparency and a clearer understanding of the decision-making process.

Opportunities to Apply More Structured Approaches to Support Benefit-Risk Assessments

FDA's benefit-risk assessments take many forms, depending on the decision problems and regulatory actions under consideration. For example, benefit-risk assessments may be needed for key decisions like the approval of a vaccine, the assessment of post-marketing safety issue for a drug on the market, or the evaluation of a novel treatment for a condition that already has other treatment options. FDA may also need to make a range of relatively smaller decisions in the course of these assessments, such as whether it should grant accelerated approval based on a surrogate endpoint, what information should be included in a label, and whether there should be risk management requirements for a drug. At base, benefit-risk assessment is a process, and it involves certain key steps: 1) framing the decision problem; 2) characterizing benefits, risks, and uncertainties; 3) weighing benefits and risks; and 4) including patient input during the first three steps where appropriate. Correspondingly, each step in the process can be supported by a spectrum of qualitative and quantitative tools. In any given situation, FDA must consider what approach is needed, if the approach is feasible, and whether it is fit-for-purpose (i.e. if it fits within FDA's regulatory context and current business processes).

When a benefit-risk decision is straightforward, more qualitative tools are generally sufficient to support FDA's regulatory decision. However, when there is greater uncertainty about whether the product's benefits outweigh its risks, or when there may be differing perspectives among stakeholders, more quantitative methods may be able to offer additional insight that can support decision-making. A range of tools can be employed, including value trees, flow charts, influence diagrams, effects tables, forest plots, probability distributions, multi-criteria decision analysis (MCDA), and sensitivity analyses, among others.

There is some, albeit limited in scope, experience using more quantitative and decision-analytic approaches to support FDA's decision-making. For example, for several years, CBER has had a dedicated staff conducting quantitative assessments of this nature. (For example, please see transcript of the 102nd Blood Products Advisory Committee, pages 52-73.) Their experiences utilizing these tools provide context for how quantitative and decision-analytic approaches could potentially be included within formal decision-making processes in FDA.

These more quantitative and decision-analytic approaches to benefit-risk assessment have the potential to improve the quality of internal deliberation by structuring the discussion, help reviewers evaluate the benefits and risks of different policy options, and improve the communication and transparency of challenging decisions. However, participants did emphasize that considerable resources are required to complete these assessments. While CBER has plans to build tools and templates to speed up this process and increase efficiencies over time, some major quantitative benefit-risk assessments conducted by CBER have taken as long as a year. While there are constraints, overall quantitative benefit-risk assessment has been successful at informing decision-making in CBER.

Utilizing Quantitative Methods to Characterize Uncertainties and Weigh Benefits and Risks

The bulk of the day's discussion centered on the potential benefits and challenges of using more quantitative methods for benefit-risk assessment as a formal part of FDA's Benefit-Risk Framework. Participants reiterated the potential benefits of the tools and methods already in use at FDA, but also articulated other benefits of using these methods. For instance, the process of using these methods forces reviewers to organize all the available evidence in one place, explain their assumptions, and compare those with the assumptions of others who are involved in the decision-making process. This approach can better help reviewers recognize where they are making assumptions in the face of uncertainties, and understand the impact of uncertainties on their decision, prompting them to think more systematically about the problem.

These approaches can also prompt the use of quantitative expressions to help focus the conversation, as words alone may yield a lack of precision. If someone, for example, indicates that they are "mostly certain" about an outcome, that level of certainty may reflect a 90% level of certainty to one person, while indicating a 70% level of certainty to another. These differences in interpretation may lead to conflicting determinations on next steps. Using numbers to talk about uncertainty can help clarify what level of certainty each participant brings to the decision-making.

Quantitative and decision-analytic methods can help reviewers understand the logical flow of factors being considered, and may also provide reviewers a means to actually estimate the likelihood or magnitude of expected benefit and harm to patients in the post-market setting under different assumptions. Moreover, these methods may help reviewers understand what inputs are having the biggest impact on the analysis. Participants did emphasize, however, that these processes mostly do not involve the formal weighing of benefits and risks. Instead, these methods can enable reviewers to see the distribution of benefits and risks. They then rely on expert judgment to make the final decision.

Outstanding Questions and Potential Next Steps for Using Quantitative Methods for Benefit-Risk Assessment

Despite the potential of these methods, participants noted a number of constraints that may limit their value or feasibility, including the resource-intensive nature of the process. Lacking the standing capacity to take this approach for every decision, it was considered important to determine when quantitative decision-analytic methods would be most useful and worth the investment of resources. For example, a quantitative decision-analytic approach might be considered to yield greatest value for novel, complex, and otherwise non-straightforward decisions. However, in the context of regulatory review of submitted new drug applications, with rather tight FDA-committed timeframes for review and decision, there may be non-straightforward cases suggesting value for decision analysis where the circumstances do not offer sufficient time. It is also challenging to distinguish in advance what approach or method to use, and attempting multiple approaches further compounds the resource-intensive nature of the process. The agency would also need to devote additional time and resources to training reviewers to effectively use them. Even with an understanding of these methods, reviewers may be uncomfortable expressing uncertainty about their estimates.

Finally, participants emphasized that quantitative analyses come with their own set of inherent challenges, including the potential for incorporating biases or obscuring value-laden assumptions.

Utilizing more involved quantitative analyses may also prove challenging for communicating the results of FDA's decision-making to a broader audience.

In order to move forward with utilizing quantitative methods more widely within the Benefit-Risk Framework, participants considered that a number of steps first need to take place. A primary task would be determining when these methods are appropriate and worth the resource and time investment. For most decisions, the assessment of risks and benefits was considered to be fairly straightforward and, as noted above, the current qualitative approach would be sufficient. However, quantitative decision analytic methods may be useful for a small subset of cases (likely less than 10%) where there is greater uncertainty, divergent assumptions, and internal disagreement.

For these types of approaches to be integrated into formal processes, participants considered that reviewers and researchers would need a set of tools they could use to guide them. Correspondingly, some suggested that standards may be needed to ensure consistency in approach to decision-making and clear communication of how these tools were used. It may be valuable to pilot certain approaches or have case studies available to assist reviewers when employing these methods. It was also noted that reviewers may already be making implicit value judgments about the relative importance of benefits and risks throughout their decision-making, and it could be valuable to encourage reviewers to be more explicit about these judgments where appropriate. FDA would also need to build capacity to more routinely apply these methods and still operate within established review timelines.

Participants also underscored the need for a reframing of how stakeholders (both internal and external) perceive these methods. First, there is not necessarily a binary divide between qualitative and quantitative methods; rather, there is a spectrum of approaches, many of which include quantitative and qualitative elements. Moreover, some participants expressed concern that employing quantitative methods would require reviewers to formally weigh benefits and risks against each other on the same scale. Others indicated unease with having to calculate a final number that would indicate whether they should approve a drug. While this is not how quantitation is typically used, the agency may want to consider how best to communicate internally about these methods to ensure faster acceptance.

Incorporating Patient Input into Benefit-Risk Assessment

The last session of the workshop focused on the opportunities and challenges of incorporating patient input more formally into FDA benefit-risk assessments. Participants first emphasized the difference between two key types of patient input: patient preferences and patient-reported outcomes (PROs). PROs[8] are a type of clinical outcome assessment that capture a patient's self-report of their experiences and are used to assess the patient's current health state or the clinical effects that a drug may provide. For example, pain and fatigue are clinical outcomes that can be measured using PROs. In contrast, patient preferences reflect what patients want from a treatment and the risks they are willing to accept from that treatment in exchange for that benefit. While clinical outcome assessments like PROs are routinely used to support agency decision-making, CDER and CBER have relatively less experience with patient preference information. Discussion at the workshop focused primarily on the benefits and challenges of using methods to elicit patient preference information.

Participants noted that patient preference information can inform drug development in a number of different ways. It can, for example, be used to identify the benefit and risk attributes that matter to patients (in other words, *what* matters to patients), assess the relative importance of those attributes to

patients (in other words, *how much* each attribute matters to patients), and evaluate what tradeoffs patients are willing to make to obtain or avoid a given attribute. Such information has the potential to inform researchers how patients experience the burden of a disease, elicit the value patients place on a given treatment outcome, identify areas of unmet medical need, and weigh potential outcomes. Patient preference information also adds to the overall body of evidence on a drug and provides a more complete picture of how a drug impacts patients' lives. It can also be an important component in benefit-risk decisions, particularly when such decisions are challenging.

Outstanding Questions and Potential Next Steps Regarding the Use of Patient Preference Information

Although many participants recognized its potential, some expressed concerns over incorporating patient input, in the form of patient preference studies, into the formal Benefit-Risk Framework. It was unclear, for example, what the standards and principles are for conducting such studies. The potential biases that can be introduced are large, and there is room for the manipulation of results based on how these studies are conducted. Participants also noted that patient selection is a crucial component of this process. Patients selected for these studies must be representative of the patient population at large, but there was uncertainty on whether that was possible for most studies. More broadly, participants wondered how best to systematically incorporate patient input, of any kind, into the benefit-risk decision and how to determine what kind of weight it is given in the overall assessment of benefits and risks.

In order to consider incorporating patient input the Benefit-Risk Framework, participants suggested that the agency should consider several outstanding issues. Participants underscored that there should be standards for how to include patient input in the Benefit-Risk Framework. Currently there is no consensus on the standards for evidence that can be used in this type of decision-making. This includes patient selection for these studies, which can have a large impact on the results.

As a starting point for tackling some of these issues, some participants recommended looking to the experiences of the Medical Device Innovation Consortium (MDIC) and the Center for Devices and Radiological Health (CDRH) for direction. MDIC recently produced a framework for incorporating information on preferences into benefit-risk assessments of new medical technology[9], and CDRH and CBER have issued guidance on how to incorporate patient preference information into premarket applications for devices.[10] These documents could be a useful starting point for how these standards might be established.

Major Takeaways and Areas for Future Research

The day ended with a broader discussion of themes and next steps. The following key themes were identified:

1. Though formal quantitative or decision analytic methods are not needed in most benefit-risk assessments, they may be useful in certain cases, particularly when there is uncertainty about whether the product's benefits outweigh its risks, or when there may be differing perspectives among stakeholders.

2. Given the additional time and resources required to use these methods, FDA will need to develop a process and internal guidelines for determining when they should be applied, which

methods or tools should be used, and how the results should be interpreted (i.e., how they can be made fit-for-purpose).

3. Where applied, these methods should not replace reviewers' judgments, but rather should support them. Their value is often in the process, rather than the final 'number'.

Potential Next Steps to Advance the Benefit-Risk Framework

Strengthening the Current Benefit-Risk Framework

- Consider the inclusion of data visualizations, tabular summaries, graphical summaries, and other tools
- Consider the inclusion of the patient's perspective, broadly defined, where appropriate
- Engage with reviewers to encourage the use the Benefit-Risk Framework as a decision-making tool, not just as a communication tool

Incorporating Quantitative and Decision-Analytic Methods into the Benefit-Risk Framework

- Develop a toolkit of applicable approaches, including when and how to utilize them, as well as standards for how to apply them appropriately
- Identify case studies that can illustrate the proper application of these methods

Increasing Internal FDA Capacity to Review and Use Quantitative and Decision-Analytic Methods

- Train reviewers on how to use more quantitative methods within the context of the Benefit-Risk Framework
- Build additional capacity to use and review methods, which may include recruitment to bring in the right expertise or other external engagement strategies such as outreach to PhD candidates or post-doctoral researchers.

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[1] U.S. Food and Drug Administration. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making; Draft PDUFA V Implementation Plan (2013). Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

[2] Ibid.

[3] Ibid.

[4] Earlier versions of the Benefit-Risk Framework contained five rows, with a separate row for *Risk* and *Risk Management*. As part of refinements to the Benefit-Risk Framework in 2017, FDA combined the *Risk* and *Risk Management* rows, since these two dimensions are intricately linked.

[5] Ibid.

[6] Ibid.

[7] Brennan, Z. (2017, August 21). Regulatory Explainer: FDA User Fee Reauthorizations From 2018 to 2022. August 21, 2017). Retrieved from http://raps.org/Regulatory-Focus/News/2017/08/21/28282/Regulatory-Explainer-FDA-User-Fee-Reauthorizations-From-2018-to-2022/

[8] A PRO is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also

be observable by others. Definition from the FDA-NIH **B**iomarker, **E**ndpoint**S** and other **T**ools (BEST) Glossary; retrieved from https://www.ncbi.nlm.nih.gov/books/NBK338448/

[9] Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project Report: A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology (2015). Retrieved from http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf

[10] U.S. Food and Drug Administration. Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling (2016). Retrieved from https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf