

Characterizing FDA’s Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

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Background Document

Introduction

Drug approvals depend on determinations that new drugs are safe and effective for their intended use based on evidence from adequate and well-controlled studies. The U.S. Food & Drug Administration (FDA) has interpreted “safe and effective” to mean that benefits outweigh risks. In order to increase the predictability, transparency, and efficiency of its decision-making process, FDA developed and is implementing a Benefit-Risk Framework. According to FDA, the goals of this framework are (1) to improve clarity and consistency in communicating the reasoning behind drug regulatory decisions, and (2) to ensure that FDA reviewers’ detailed assessments can be more readily understood in the larger patient care and public health context.¹ In support of these goals, the Agency began work in 2013 to incorporate structured benefit-risk assessment into the human drug review process.

FDA’s benefit-risk framework was developed to support decision-making throughout the product life cycle and benefit-risk considerations play a key role in preclinical data collection, clinical development, FDA review, and postmarketing. In 2017, under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI), FDA committed to furthering the Agency’s implementation of its Benefit-Risk Framework (BRF) in the human drug review process. As part of this effort, FDA committed to participating in a public meeting conducted through a qualified third party to gather industry, patient, researcher, and other stakeholder input on applying the BRF throughout the drug life cycle and best approaches to communicating FDA’s benefit-risk assessment. Accordingly, the Duke-Margolis Center for Health Policy is convening a public meeting on May 16, 2019, under a cooperative agreement with FDA, to solicit broad stakeholder input on FDA’s approach to benefit-risk assessment and its upcoming draft guidance on the topic.

History of the FDA Benefit-Risk Framework

In 2009, FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) began exploring approaches to the development of a framework that could increase clarity and consistency in communicating key benefit-risk considerations supporting FDA’s regulatory decision-making.² FDA determined that a qualitative framework could most effectively support decision-making and communication while remaining sufficiently flexible to incorporate quantitative benefit-risk information.³

Initial work toward a qualitative framework began with a review of FDA’s prior regulatory decisions, across the product life cycle, to understand factors contributing to FDA’s analysis of a products’ benefit-risk balance. 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. Following continued refinement of the Benefit-Risk Framework under PDUFA V and PDUFA VI, FDA began in 2017 to systematically integrate the Benefit-Risk Framework into the drug review process for New Drug Applications (NDAs), Biologics Licensing Applications (BLAs), and many types of efficacy supplements.⁴

The Benefit-Risk Framework (Figure 1)⁵ consists of Benefit-Risk Dimensions (Figure 1, top) which are key decision-support factors that provide the foundation for the assessment⁶; as well as a section on Conclusions Regarding Benefit-Risk (Figure 1, bottom), which provides a summary analysis of how key decision elements were weighed. The conclusion section articulates an explanation for the Agency’s final regulatory decision. These two elements allow the Benefit-Risk Framework to serve as both a decision-making and communication tool. This framework is used in part to organize and standardize the Agency’s review of a product’s benefit-risk balance as well as to facilitate effective communication of benefit-risk information between FDA review teams, sponsors, and the general public. According to FDA, a systematic approach that specifies the sources and the strength of evidence and articulates how the uncertainty is weighed, can also lead to more explicit communication of postmarket regulatory decisions.⁷ Under the authorization of PDUFA VI, the Agency is particularly committed to enhancing the systematic application of benefit-risk assessment in postmarket review.⁸

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

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

Patient Focused Drug Development and Benefit-Risk Assessment

Patients are uniquely positioned to inform regulatory understanding of the therapeutic context for drug development and evaluation. Patient experience data can be used to support trial design, can be collected throughout product development, and can also be leveraged for use in benefit-risk assessment and regulatory review.⁹ Information on how patients experience disease symptoms can provide valuable insight about the clinical context of a disease to sponsors and FDA review teams alike. Additionally, the collection of preference and risk tolerance information from patients can be used to understand the benefits of new products and therapeutic alternatives and is particularly useful in regulatory decision-making for products with complex benefit-risk considerations.¹⁰

Accordingly, FDA has been implementing a systematic approach to facilitate the collection and meaningful incorporation of patient and caregiver input into regulatory decision-making.¹¹ Beginning in 2012 under PDUFA V, FDA began conducting multiple disease-specific patient focused drug development (PFDD) meetings to gather information on the patient perspective and experience. By the end of 2017, twenty-four FDA-led meetings had been conducted and the Agency had formally introduced a mechanism for externally-led PFDD meetings to inform FDA decision-making in additional disease areas.^{12,13} FDA continues to advance PFDD through 21st Century Cures and PDUFA VI commitments, which require that FDA develop multiple guidances on the collection and use of patient experience data.¹⁴

The value of patient input is also recognized by the pharmaceutical industry and, accordingly, sponsors have undertaken the evaluation of several approaches to the solicitation and use of patient experience data in product development.¹⁵ Sponsors are exploring the use of methodologies and tools to obtain and integrate patient input including, preference assessments, patient reported outcome (PRO) measures, and discussions with patient advocacy groups.¹⁶ Each of these tools has utility in the collection of patient experience data and should be designed and implemented to capture data from heterogeneous target populations with a mix of differing preferences. Consideration of patient preferences in benefit-risk assessment must account for the fact that the interpretation of benefit and risk is subjective and risk tolerance may differ amongst patients, providers, sponsors, and regulators.

Next Steps for FDA Benefit-Risk Assessment

Benefit-risk assessment is foundational to drug development, review, and regulation, and FDA's benefit-risk framework helps support this assessment throughout the drug lifecycle. FDA has made progress with respect to the systematic integration of the benefit-risk framework in its regulatory decision-making process—over 87% of the product review documents assessed by a third-party evaluator contained a benefit-risk framework.¹⁷ The Agency's completed benefit-risk frameworks also received, on average, good or excellent ratings for clarity in the same third-party evaluation.¹⁸

FDA will continue the implementation and refinement of its benefit-risk framework in part by undertaking initiatives to incorporate the patient voice in decision-making and by improving the accessibility and clarity of benefit-risk assessment. As part of this continued refinement, FDA will continue exploring quantitative or formal decision-analysis approaches with the potential to add value to the Agency's benefit-risk assessment, particularly for products with complex benefit-risk considerations.¹⁹ For example, quantitative methods may be able to provide additional insight to

support decision-making when there are significant uncertainties about a product's benefit-risk profile, benefits and risks are difficult to compare, heterogeneous effects are anticipated or observed for different patient subgroups, or there are many different (and potentially conflicting) sources of benefit-risk information to consider. Going forward, the Agency will continue to implement a quantitative benefit-risk module as part of training for the review of biologics and will take steps towards the evaluation and provision of quantitative tools (such as value trees, forest plots, and quantitative benefit-risk assessment models) for use in broader, agency-wide efforts.²⁰ Finally, as part of PDUFA VI, the Agency has committed to enhancing the implementation of its benefit risk framework in the postmarket setting and to issuing draft guidance to clarify key benefit-risk considerations weighed throughout the product life cycle.

¹ U.S. Food and Drug Administration, "PDUFA VI Implementation Plan: Benefit-Risk Assessment in Drug Regulatory Decision-Making."

² U.S. Food and Drug Administration, "PDUFA V Implementation Plan: Structured Approach to Benefit-Risk Assessment In Drug Regulatory Decision-Making."

³ Duke University, Robert J. Margolis, MD, Center for Health Policy, "Structured Benefit Risk Assessment Meeting Summary."

⁴ U.S. Food and Drug Administration, "PDUFA VI Implementation Plan: Benefit-Risk Assessment in Drug Regulatory Decision-Making."

⁵ Biotechnology Innovation Organization, "A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework."

⁶ U.S. Food and Drug Administration, "PDUFA V Implementation Plan: Structured Approach to Benefit-Risk Assessment In Drug Regulatory Decision-Making."

⁷ U.S. Food and Drug Administration, "PDUFA V Implementation Plan: Structured Approach to Benefit-Risk Assessment In Drug Regulatory Decision-Making."

⁸ U.S. Food and Drug Administration, "PDUFA VI Implementation Plan: Benefit-Risk Assessment in Drug Regulatory Decision-Making."

⁹ U.S. Food and Drug Administration, "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input."

¹⁰ 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"

¹¹ CDER Patient-Focused Drug Development.

<https://www.fda.gov/drugs/developmentapprovalprocess/ucm579400.htm>

¹² Patient-Focused Drug Development: Disease Area Meetings Held in Fiscal Years 2013-2017.

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm>

¹³ Externally-led Patient-Focused Drug Development Meetings.

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm>

¹⁴ FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making.

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610279.htm>

¹⁵ European Medicines Agency, "The Patient's Voice in the Evaluation of Medicines."

¹⁶ Biotechnology Innovation Organization, "A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework."

¹⁷ U.S. Food and Drug Administration, "Public Meeting on Benefit-Risk Assessments in Drug Regulatory Decision-Making."

¹⁸ Ibid.

¹⁹ "Duke University, Robert J. Margolis, MD, Center for Health Policy, 'Structured Benefit Risk Assessment Meeting Summary.'"

²⁰ U.S. Food and Drug Administration, “PDUFA VI Implementation Plan: Benefit-Risk Assessment in Drug Regulatory Decision-Making.”