

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

Convening Summary
Benefit-Risk Public Meeting—May 16, 2019
Benefit-Risk Stakeholder Teleconference—August 26, 2019

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INTRODUCTION

With the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA VI), the U.S. Food and Drug Administration (FDA or Agency) has committed to furthering its implementation of structured benefit-risk assessment (BRA) in medical product review and enhancing the integration of patient input in regulatory decision-making, according to the Agency's PDUFA VI implementation plan.ⁱ As part of this commitment, the Agency will issue draft guidance on its approach to BRA. This guidance will articulate, in part, how key benefit-risk considerations about a drug's benefits, risks, and risk management options inform BRA and how the Agency's benefit-risk framework (BRF) supports and structures decision-making related to market authorizations for medical products. Additionally, the guidance will discuss how relevant patient experience data and related information may be used to inform BRA. As part of its PDUFA VI implementation plan, the Agency also committed to collect and consider stakeholder input on approaches to communicating BRA information to biopharmaceutical industry stakeholders (developers) and the public.ⁱⁱ

Accordingly, under a cooperative agreement with the FDA, the Duke-Margolis Center for Health Policy (Margolis Center) convened a public meeting in May 2019 to facilitate discussion on the implementation and communication of the FDA's BRF. Following the public meeting, the Margolis Center sought to address additional questions related to benefit-risk approaches and convened a follow-on teleconference. Varied industry stakeholders participated, as well as Agency colleagues involved in planning the public meeting. The follow-on teleconference focused on industry stakeholders' decision-making related to overall BRA, internal benefit-risk communication practices, and approaches to communicating benefit-risk information with the Agency. See the accompanying Appendix for the public meeting agenda and a list of discussion questions developed for the follow-on teleconference. The following is a summary of considerations and recommendations discussed at these convenings that the Agency can consider during guidance development and the ongoing implementation of the BRF. This summary describes input from a broad range of stakeholders who attended the public meeting, including regulatory, industry, patient and academic stakeholders, as well as input from industry stakeholders who participated in the follow-on teleconference.*

BACKGROUND ON THE FDA'S BENEFIT-RISK ASSESSMENT FRAMEWORK

According to FDA's PDUFA V implementation plan, the Agency began work towards the implementation of a structured BRF in 2009 in an effort to better structure and improve transparency in regulatory decision-making and address feedback on the ongoing conduct of benefit-risk assessment in medical product review.ⁱⁱⁱ The FDA approached the development of its BRF by studying past regulatory decisions and instituted a basic structure for the framework that incorporated five key decision factors—analysis of condition, current treatment options, benefit, risk, and risk management.^{iv}

At the public meeting, FDA representatives reported that the Agency is taking steps to modernize its New Drugs Regulatory Program and enhance the implementation of its BRF. The Agency is implementing a new, issue-based integrated assessment for the interdisciplinary review of marketing applications, with an explicit focus on incorporating the patient perspective and tracking benefit-risk decisions to

* Stakeholder input has been summarized but does not necessarily reflect consensus views among public meeting and follow-on teleconference participants, nor official positions of the U.S. Food and Drug Administration (FDA).

improve internal consistency and operational efficiency. FDA representatives also stated that as the Agency continues to refine and expand the use of its BRF, its efforts will focus on enhancing the clarity and consistency of completed assessments, leveraging the BRF in the post-market setting, and continuing internal training related to the framework.^v

STAKEHOLDER INPUT ON THE IMPLEMENTATION AND COMMUNICATION OF THE FDA'S BENEFIT-RISK ASSESSMENTS

The public meeting and follow-on teleconference focused on three key topics:

- I. Factors contributing to industry and FDA decision-making related to BRA throughout the product lifecycle.
- II. The value of patient input in BRA and approaches to the elicitation and meaningful incorporation of patient experience data.
- III. The ideal scope and structure of communication between developers, the FDA, and the public regarding BRA and a product's benefit-risk profile.

The following summarizes input from meeting participants on these key topics.

I. Approaches to Benefit-Risk Decision-Making Throughout the Product Life Cycle

Participants at both convenings reported that to support pre-market development, regulatory approval, and continued BRA post-approval, benefit-risk information should be collected and assessed throughout the product life cycle. Participants emphasized that early integration of benefit-risk considerations can help developers align preclinical study design and data collection approaches with therapeutic context and medical need and can potentially support the likelihood that an investigational drug will reach a favorable BRA. At the public meeting, FDA representatives noted the Agency's BRF is the foundation of regulatory review, and continued BRA in the post-market setting is important to medical product use in the clinical setting, especially if safety issues are reported.

Benefit-Risk Assessment in Pre-Market Development

Industry participants explained during the teleconference that BRA is, in part, pre-specified in the early phases of trial design and, in part, a post-hoc exercise that takes place the end of data collection in Phase 3 and before the submission of a marketing application. Almost all participants at both meetings, recommended that planning for industry-conducted BRA begin early in the product development lifecycle, and most industry participants reported that they do consider how their clinical programs will interface with the four dimensions of the FDA's BRF towards the beginning of the pre-market development phase. Industry participants noted during both the public meeting and follow-on teleconference that the impact of several trial design factors—including endpoint choice and dose—on BRA depends greatly on therapeutic context and in some cases patient risk preferences which are also used to characterize benefit and risk.

To ensure the design of clinical programs that support a favorable benefit-risk balance, industry participants stated that they consider information about the natural history, pathophysiology, and severity of the disease or condition which can inform several components of trial design, including the identification of a target population and dose selection, and can ensure minimized risk and maximized

product benefit in the target population. To further inform BRA, industry participants specified during the teleconference that they may also conduct an analysis of existing therapies, their shortcomings (for example, effectiveness, tolerability, and other factors), potential comparators, and unmet medical need during pre-market development. Therapeutic context significantly impacts a product's benefit-risk profile. Stakeholders at the public meeting stated that, in the context of rare diseases or conditions for which there are unmet medical needs, evidence of a modest benefit may be amplified in the assessment if it represents an improvement over standard of care. Relatedly, stakeholders stated that evidence of a benefit may be weighed differently, however, during product development for common conditions for which there are multiple existing therapeutic options.

Stakeholders at both meetings also discussed the clinical relevance of study endpoints, including the relationship of surrogate endpoints to clinical outcomes of interest, and how both clinical and surrogate endpoints factor into benefit-risk decision-making early on in pre-market development. Industry participants reported during the teleconference that endpoint selection is the trial design factor with the most significant impact on BRA and that the predicted magnitude and duration of the anticipated clinical benefit greatly informs a product's benefit-risk balance. Industry participants also noted that endpoints selected for use in BRA are often derived by combining efficacy endpoints and safety endpoints. Because this method can introduce complications related to double counting, causal dependency, and different timeframes for measurement, developers may consider the identification of a new set of benefit-risk endpoints or the continued refinement of selected endpoints as product development proceeds. Developers have several tools at their disposal to define and evaluate clinical benefit and to select the most clinically important endpoints for integration into a BRA. For example, industry participants reported that they may leverage value tree modeling as part of multi-criteria decision analysis (MCDA), which is informed by several data points, including patient input, a vital tool in the characterization of meaningful benefit and, as such, paramount to the identification of endpoints associated with advancements in disease treatment.

Benefit-Risk Assessment and the Evaluation of Marketing Applications

According to the Agency's PDUFA VI implementation plan, their BRF is foundational to the review and evaluation of marketing applications for medical products, and to the communication of regulatory decisions made by the Agency.^{vi} At the public meeting, FDA participants discussed the utility of the BRF as a tool to structure the systematic analysis and presentation of a product's benefit-risk profile, given the multi-disciplinary nature of the review teams as well as the volume and complexity of the data that reviewers consider. FDA participants also reported that the BRF serves as a useful tool for understanding and communicating each data point in the context of drug review and a mechanism for the Agency to track issues in product review from pre-NDA to application submission.

Meeting participants discussed the use of different methods at the Agency to frame the conduct of a product-specific BRA. FDA participants stated that they typically conduct population-level BRA to understand absolute treatment effects (in some cases, trial design and data collection characteristics may preclude anything but a population-level analysis). FDA participants, industry participants, and other meeting participants also discussed the utility of tools such as value-trees and influence diagrams (flow charts) in guiding BRA and regulatory decision-making. Further, participants discussed the use of heatmaps to assess the totality of evidence by illustrating how different patient subgroups experience primary, secondary, and tertiary endpoints and also to determine how clinical benefit can be articulated

through labeling for specific patient populations. Additionally, participants discussed the utility of forest plots when benefits and risks can be compared on the same, well-defined scale.

Importantly, industry and FDA participants discussed how implementation of the FDA's BRF may be enhanced and how BRA conducted by developers can better align with the BRF used by the Agency during regulatory review. This discussion centered around expectation setting and information sharing, and industry participants articulated a need for additional information regarding the type and scope data that is most important for benefit-risk assessment, as well as the level of detail needed by the Agency to facilitate decision-making. Industry participants noted that the need for additional information stands to become increasingly important with the addition of more, and more complex, patient-generated data in development programs, and thus BRA included in marketing applications.

Post-Market Benefit-Risk Assessment

A majority of industry participants noted at both convenings that the benefits of a treatment are typically well characterized during pre-market clinical trials and developers don't often encounter significant new benefit information for the approved indication in the post-market setting. However, new information about the risks of a product and adverse event information accumulates as product use in the clinical setting is monitored. Industry participants stated that as new information accrues in the post-market setting, with more patients exposed to a treatment, safety signals can become amplified. Industry participants emphasized that this information was important to consider in context and when assessing a product's benefit-risk balance in the post-market setting they account for several factors including product-specific data, standard of care, availability of other treatments, tolerance for uncertainty, and the tradeoffs related to the product's benefit-risk balance, each of which can vary according to clinical circumstances. In cases where safety findings indicate an issue with a marketed product, developers also consider the severity of risk as well as the frequency and reversibility of the issue when evaluating the implications of the issue for benefit and risk profile. Given that sources of evidence are sometimes less rigorous in the post-market setting—adding uncertainty to whether a safety signal is associated with the drug—industry participants reported that they evaluate the rigor and quality of emerging safety data when attempting to determine if a causal relationship exists between the product and safety signal. For example, polypharmacy is a common and complicating factor in the post-market setting and may impede the reliable interpretation safety signals. Accordingly, developers assess the need for continued monitoring or other risk-mitigating actions, as well as the need to reassess a product's benefit-risk balance, when a safety signal arises.

Depending on the results of this assessment, industry participants stated that they may consider the necessity of a labeling change or may choose simply to update core data sheets and regional prescribing information. Meeting participants also discussed situations in which developers and regulators may consider the initiation of a risk evaluation and mitigation strategy (REMS), boxed warning, or, with the occurrence of more serious safety signals, the conduct of a structured BRA via a Periodic Benefit Risk Evaluation Report (PBRER). Industry participants acknowledged the value of including structured BRA within PBRERs as well as the utility of safety signals in the continuous assessment of a product's benefits and risks, but some noted the need for additional guidance with respect what events or new information might trigger the conduct of a structured BRA after a product reaches the market. Industry participants also noted that incomplete harmonization between the FDA PBRER and the ICH E2C

guidelines can complicate the articulation of benefit-risk information in a global context, especially where patient and prescriber preferences may differ regionally.

BRA in the post-market setting can be informed by data from numerous sources, including clinical trials, real world evidence studies, new PKPD studies, new information in the literature (for example, case reports and meta-analyses), and spontaneous reports from patients or health care providers submitted to the FDA or developers. Industry participants noted, however, the need for additional guidance on when and how, to engage with the FDA when new information becomes available in the post-marketing setting. Industry participants also acknowledged that quantitative approaches to BRA (for example, multi-criteria decision analysis) may supplement qualitative decision-making in the post-market setting, but noted that more guidance on valid methods for quantitative BRA as well as more information on what type of quantitative data is useful to post-market decision-making is needed.

II. Opportunities for Effective Integration of Patient Input in Benefit-Risk Assessment

The majority of meeting participants noted that because patient priorities and preferences help to define what benefits and risks matter and how much, and what trade-offs may be generally acceptable given disease experience and therapeutic context, developers are encouraged to design clinical programs around benefit-risk considerations and endpoints that are directly relevant and impactful to patients. Operationalizing patient input in BRA may require modifying study design and data collection methods in the pre-market phase of drug development. Accordingly, almost all meeting participants recommended that developers seek patient input early on and incorporate it throughout product development. Meeting participants noted that patient input should also be solicited during the post-marketing phase of development as patient experience and outcome information accrues and may differ from the information collected during clinical study.

Elicitation Methods for Patient Input

Public meeting participants identified a number of useful methods for patient preference elicitation in the pre-market setting (for example, patient advisory boards, patient preference studies, patient reported outcome (PRO) tools, and social media listening) but noted that there is wide variation in terms of how patient information is collected across drug development programs. Patient preferences can also vary greatly within the same therapeutic context. For example, meeting participants noted that some patients may value increased life expectancy regardless of risks associated with a drug while others may value increased quality of life over length of life. When preferences vary, it is useful to determine the magnitude of variation, whether it is a continuum of variation, or bimodal, and whether it is specific to a certain risk or benefit. Meeting participants recommended that developers and FDA reviewers account for this heterogeneity in BRA. Meeting participants also discussed the need for BRA to account for uncertainty related to patient generated data, in part, given probable underrepresentation of at-risk patients in clinical trials.

Additionally, meeting participants identified opportunities to collect and integrate patient input into post-market BRA including through FDA public meetings, PFDD meetings, patient and disease advocacy organizations, and patient registries. Meeting participants also noted that there may be opportunities to incorporate patient input in BRA through REMS design, PROs, surveys, and mobile application data as well. Meeting participants discussed the need for methods to address rapid post-approval safety

decisions and treatment heterogeneity and noted that these methods might rely on a learning healthcare system that captures data and incorporates quality of life effects to create models that can predict benefits and harms in the post-market setting.

Meeting participants discussed the need for better methodologies, perhaps through subgroup analyses, to analyze patient experience data at the individual level and translate the results of this analysis into a meaningful input for BRA in both the pre-market and post-market setting. One industry participant at our public meeting elaborated that, in the pre-market setting, there are cases when patients can tell they are responding to an investigational therapy, and there are cases when patients cannot tell and that these different circumstances alter how patients weigh risks, and how risks are reported at the population-level. As the use of formal patient preference elicitation methods increases, industry participants noted that they are also interested in guidance on what standards may be used to establish the credibility of patient preference information for the purpose of BRA. While industry participants noted gaps in the knowledge base with respect to valid and reliable patient preference elicitation methods they also highlighted the IMI-PREFER project, which shows promise in formulating expert, evidence-based recommendations on how and when patient preferences can be assessed and used to inform BRA and medical product decision-making.

Meaningful Integration of Patient Input

Patient preference and patient experience data have potential applications throughout the product development lifecycle and deliberate integration of these data better enables meaningful therapeutic innovation. Meeting participants discussed how patient data, collected early on and throughout development, can function to inform each of the four key benefit-risk dimensions. There was broad agreement at each meeting that patients are experts on the clinical aspects of their own conditions and their input is critical to helping developers characterize disease burden. Patient input collected early on is also critical in determining the goals and characteristics of the current standard of care and identifying areas of unmet need. During the public meeting and follow-on teleconference, industry participants emphasized that this information has important implications for trial design, patient selection, dose selection, duration of trials, and, critically, for the selection of endpoints in pre-market development. Additionally, feedback heard during the teleconference indicated that this holds true especially for some indications, like psoriasis or rheumatoid arthritis, where the patient perspective should be weighed more heavily because it can dictate the inclusion of endpoints that improve patient quality of life, beyond mortality and irreversible morbidity or other adverse events that can be avoided with clinical decision-making after market authorization. Finally, industry and FDA participants discussed the importance of patient input in understanding the clinical significance of decision-making regarding acceptable levels of risk and uncertainty during the design and conduct of clinical trials as well as the strengths and limitations of those trials.

III. Tools and Methods for the Communication of Benefit-Risk Information

Industry Communications with FDA

Industry and FDA participants reported that developers often solicit feedback from FDA throughout development to identify perceived gaps in the collection of benefit-risk information and to ensure that trials are optimized to generate data that meet regulatory expectations. According to the industry

participants who attended both the public meeting and follow-on teleconference, this type of feedback, typically delivered in an end-of-phase 2 meeting between the developer and FDA, can improve industry-agency alignment and may help inform the decision to move a promising compound to phase 3 development.^{vii} Industry participants noted that communication about approaches to the optimization of a product's benefit-risk balance is also beneficial while phase 3 protocols are being designed and endpoints are being determined.

At the public meeting, FDA participants noted that the Agency encourages developers to communicate with the Agency regarding benefit-risk considerations early on in product development, and in particular, when a challenging benefit-risk issue becomes apparent. However, industry participants indicated that there are no guidelines for developers regarding communications with the FDA specific to BRA, and that developing standards could better support developer and regulator decision-making. For example, industry participants stated that they may occasionally report benefit as the relative risk and its associated p-value, when, in fact, communicating the absolute benefit may be more useful for the conduct of a BRA during regulatory review. Industry participants noted that the FDA guidance outlining the scope, timing, and content for communications with the Agency about the range of potential benefit-risk considerations is an appropriate next step and that the FDA's own discussion guide for the public meeting, along with existing ICH guidance, may provide a foundation for the development of such guidance.

Patient Communications with the FDA

Meeting participants noted that channels for patients and patient groups to communicate with the FDA can be strengthened. Participants stated that patients and patient advocacy groups may provide input to the Agency through PFDD and Advisory Committee meetings, but that the Agency typically relies on developers to act as a conduit for patient input and the collection of patient preference and experience data for use in product development and review. Patient representatives at the public meeting stated that they are interested in ensuring that the correct information is reaching the current people and divisions at the Agency. Further, these representatives reported that patients would like to see their involvement in patient experience and preference studies preserved in cases where commercial interests shift and developers discontinue drug development programs. Incentives for developers to share this information with the patient community and public could insure against its potential loss of patient preference information.

The FDA's Benefit-Risk Framework as a Tool for Communication

FDA participants emphasized that the BRF is used as a tool for internal education to leverage learning from the various and multiple product reviews conducted across the Agency, as well as a mechanism to facilitate communication about the Agency's regulatory decision-making to advisory committees and the public. FDA participants noted that the BRF may be used to structure advisory committee meetings and educate advisory committee members on how data, including patient input, is being synthesized and how specific pieces of data function to inform a product's benefit-risk balance. For example, they explained that the framework can facilitate the analysis of data regarding the public health context in which a product will be used, which often constitutes an important component of FDA's BRA.

Public meeting participants noted that until the BRF modifies how the different advisory committee contributors are communicating about a product’s benefit-risk profile, its full potential has not been realized. Participants discussed approaches to enhancing the FDA’s BRF including by incorporating evidence of the readiness of an intervention for implementation—an area where patient input could contribute—and adapting to facilitate the communication of levels of evidence (as in done in clinical guidance). Meeting participants also identified opportunities to update and extend benefit-risk communications in the post-market setting as an additional area for increased utility of the framework. Industry participants and patient representatives in particular noted that enhancements to the BRF may also increase the utility of the framework as a tool for clinical decision-making and may be useful for providers in communicating benefits and risks of a product to patients. Finally, participants discussed the potential for public-private partnerships to improve communication between developers and the Agency and to shape the next generation of BRA.

CONCLUSIONS AND NEXT STEPS

Results from discussion held at each of the meetings indicate that BRA in medical product development and review should be pragmatic, fit-for-purpose, and deliberate in accounting for patient input regarding meaningful treatment outcomes and tolerance for risk and uncertainty. Meeting participants generally agreed that the FDA’s new approach to the conduct and communication of BRA, through its BRF, is a meaningful step towards the implementation of more integrated, cross-disciplinary, and clinically relevant assessments. However, industry and FDA participants as well as patient representatives noted several areas for improvement in BRF implementation and the alignment of developer-conducted BRA with the key benefit-risk dimensions articulated in the FDA framework.

As the Agency develops guidance on the topic, meeting participants noted that the Agency can consider the need for additional information on valid methods for the elicitation, analysis, and integration of patient preference information in product development and how and when developers may effectively communicate with the Agency regarding BRA, particularly in the post-market setting as new information accrues. Industry participants, in particular, state that the Agency can consider approaches to enhancing communication regarding the type of information most important for BRA, as well as the level of evidence needed by the Agency to support regulatory decision-making. Finally, as part of guidance development, participants at the public meeting and follow-on teleconference recommend that the Agency consider how benefit-risk information can be best presented with the BRF. Participants recommended considering how the framework can facilitate the solicitation of feedback from the FDA throughout product development to identify perceived gaps in the collection of benefit-risk information and to ensure that a trial is optimized to generate data that meet statutory requirements and regulatory expectations.

ⁱ U.S. Food and Drug Administration. Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA VI Implementation Plan (FY 2018-2022). <https://www.fda.gov/media/112570/download>. Published March 30, 2018. Accessed June 26, 2019.

ⁱⁱ Ibid [at Draft PDUFA VI Implementation Plan]

ⁱⁱⁱ U.S. Food and Drug Administration. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan – February 2013 Fiscal Years 2013-2017. <https://www.fda.gov/media/84831/download>. Published February 2013. Accessed June 26, 2019.

^{iv} Ibid [at Draft PDUFA V Implementation Plan]

^v Ibid [at Draft PDUFA VI Implementation Plan]

^{vi} Ibid [at Draft PDUFA VI Implementation Plan]

^{vii} Biotechnology Innovation Organization, “A Lifecycle Approach to FDA’s Structured Benefit-Risk Assessment Framework.”