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# BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING

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Draft PDUFA VI Implementation Plan (FY 2018-2022)

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U.S. FOOD AND DRUG ADMINISTRATION

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## I. Introduction

As part of the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) under Title 1 of the FDA Reauthorization Act of 2017, FDA committed to furthering the Agency's implementation of structured benefit-risk assessment into the human drug review program.<sup>1,2</sup> In fulfillment of one of these commitments, FDA is publishing an update to the 2013 implementation plan titled "[Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making](#)."<sup>3</sup>

Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics.<sup>4</sup> In PDUFA V, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics and Research (CBER) committed to further our efforts to enhance benefit-risk assessment and communication in the human drug review process in Fiscal Years (FY) 2013–2017.<sup>5,6</sup> These commitments and our achievements in meeting them are discussed in Section III of this document. The keystone commitment in PDUFA V was to implement FDA's Benefit-Risk Framework (BRF) into our regulatory review processes and documentation. Background on the BRF is presented in Section II. FDA also committed to initiating a third-party evaluation of FDA's implementation of the BRF. Section VI presents a summary of that evaluation.

Enhancing and communicating benefit-risk assessment continues to be an Agency priority in PDUFA VI.<sup>7</sup> FDA has made several commitments in PDUFA VI for continued implementation of structured benefit-risk assessment during FY 2018–2022. These commitments include participating in a meeting to gather stakeholder input, publishing a draft guidance on benefit-risk assessment for new drugs and biologics, continuing to revise relevant Manuals for Policies and Procedures (MAPPs) and Standard Operating Practices and Procedures (SOPPs) to incorporate benefit-risk assessment approaches, and conducting a second evaluation of the implementation of the BRF beginning in 2021. These commitments are discussed in Section V. In addition to these commitments, FDA plans to explore additional opportunities to enhance our use and communication of benefit-risk assessments, which are discussed in Section VI.

The 21<sup>st</sup> Century Cures Act (Cures Act), which was signed into law on December 16, 2016, requires the Agency to issue guidance describing how FDA anticipates incorporating relevant patient experience data and related information into the structured benefit-risk assessment framework to inform regulatory decision-making. This implementation plan therefore integrates activities relating to the BRF under both the Cures Act and PDUFA VI.

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<sup>1</sup> See Section J.2 in the PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022: <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>

<sup>2</sup> Drugs include biological products in this document.

<sup>3</sup> See <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>

<sup>4</sup> For simplicity, the term "drug" is used in this document to mean both drugs and biologics.

<sup>5</sup> See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 at <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>

<sup>6</sup> The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, includes the fifth authorization of the Prescription Drug User Fee Act (PDUFA V). For more information on FDASIA, see here: <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAAct/FDASIA/default.htm>

<sup>7</sup> PDUFA VI was included as part of the FDA Reauthorization Act of 2017 (FDARA) which was signed into law in August 2017.

FDA welcomes public comment on this implementation plan through a public docket.<sup>8</sup> Throughout PDUFA VI, FDA will update this document as necessary and publish updates on the FDA website.<sup>9</sup>

## II. Background on FDA’s Benefit-Risk Framework

FDA’s general approach to drug regulatory decision-making is articulated in the Introduction and Section 1 of the 2013 Plan. Simply put, for a drug to be approved for marketing, FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This assessment is informed by an extensive body of evidence about the drug’s safety and efficacy submitted by an applicant in a New Drug Application (NDA) or Biologics Licensing Application (BLA). This assessment is also informed by a number of other factors, including: the severity of the underlying condition and how well patients’ medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the postmarket setting; and whether risk management tools are necessary to manage specific risks. FDA’s decisions also must reflect applicable laws and regulations.

Stakeholders have long stressed the importance of clarity and transparency of the key considerations that factor into FDA’s regulatory decision-making. In 2009, CDER and CBER began developing a structured framework to support review staff and decision makers in their effort to complete and communicate benefit-risk assessments that inform their regulatory recommendations and ultimate decisions. The goals of this framework were (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. Further background on FDA’s development of the BRF can be found in Section X of the 2013 Plan.

The Benefit-Risk Framework (Figure 1) is a structured, qualitative approach focused on identifying and clearly communicating key issues, evidence, and uncertainties in FDA’s benefit-risk assessment and how those considerations inform regulatory decisions. The BRF has two key elements. The Benefit-Risk Dimensions portion (Fig 1, bottom) outlines the critical elements (*Analysis of Condition, Current Treatment Options, Benefit, and Risk and Risk Management*) that factor into the benefit-risk assessment.<sup>10</sup> The table includes columns for outlining detailed treatment of the evidence and uncertainties as well as the conclusions and reasons for each dimension. The Benefit-Risk Integrated Assessment (Figure 1, top) ties together all the dimensions in an overall analysis and provides a succinct explanation and rationale for the regulatory recommendation or decision. The integrated assessment demonstrates how evidence and uncertainties about a drug’s benefits and risks are considered in the context of the severity of the condition and the current medical needs for patients.

As will be detailed in the next section, FDA took steps during PDUFA V to conduct a phased implementation of the BRF into the review processes for NDAs and BLAs. BRFs for approved products are posted publicly as part of the review documentation available at FDA’s [Drugs@FDA website](https://www.accessdata.fda.gov/scripts/cder/daf/). (<https://www.accessdata.fda.gov/scripts/cder/daf/>).

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<sup>8</sup> A link to the Federal Register Notice including the information about the public docket can be found here: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>

<sup>9</sup> Available at FDA’s Website: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>

<sup>10</sup> Earlier versions of the BRF contained five rows, with a separate row for *Risk* and *Risk Management*. As part of our refinements in FY 2017, CDER combined the *Risk* and *Risk Management* rows, since these two dimensions are intricately linked.

Figure 1: FDA’s Benefit-Risk Framework

<b>Benefit-Risk Integrated Assessment</b>		
<b>Benefit-Risk Dimensions</b>		
<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

### III. Progress Made During PDUFA V on Benefit-Risk Assessment

In PDUFA V, FDA committed to further develop and implement the BRF into FDA’s human drug and biologic review processes. These commitments, and the progress FDA has made in meeting them, are described in this section.

**a. Develop and publish a five-year plan that describes FDA’s approach to implementing structured benefit-risk assessment in the new drug approval process**

In February 2013, FDA published a Draft PDUFA V Implementation Plan entitled “Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making.” The 2013 Plan provided background on the development of FDA’s framework for drug regulatory decision-making, the planned approach for implementation of the framework into the regulatory process, and the incorporation of PDUFA V commitments. FDA posted a notice in the [Federal Register](#) to announce the availability of the draft plan and to provide an opportunity for public comment on the draft plan.<sup>11</sup>

**b. Revise review and decision memo templates and manuals to incorporate FDA’s approach to benefit-risk assessment**

FDA’s PDUFA V commitments included revision of CDER’s Clinical Review Template, the Office and Division Director Summary Memoranda Templates, and equivalent CBER documents to incorporate structured benefit-risk assessment into the human drug review process. CBER and CDER adopted slightly different approaches to implementing the BRF into the review process.

In May 2013, CBER integrated the BRF into the review process for BLAs and supplemental BLAs in the following way: The primary clinical reviewer completes the BRF in its structured format in Section 11 of

<sup>11</sup> See <https://www.regulations.gov/document?D=FDA-2013-N-0196-0001>

the CBER BLA Clinical Review Memorandum: Risk-Benefit Considerations and Recommendations. Upon completing the full review, the review chair or signatory places his or her benefit-risk assessment (but not including the BRF table portion) in a dedicated section, usually Section 11, of the Summary Basis for Regulatory Action (SBRA).

In September 2013, CDER initiated the Benefit-Risk Implementation Committee (BRIC), composed of clinical review staff and review management across CDER's clinical review divisions, as well as policy and training experts.<sup>12</sup> The BRIC was tasked with aiding the development of revised review and memo templates incorporating the BRF. CDER first incorporated the BRF into the review templates for New Molecular Entity (NME) NDAs and original BLAs. This included four document templates: a) the Clinical Review, b) the Cross-Discipline Team Leader Review, c) the Division Director Summary Review for Regulatory Action, and d) the Office Director (the signatory authority for NMEs and original BLAs) Decisional Memo. Each subsequent level of review can draw on the previous versions to support completion of the BRF. The BRF completed by the signatory authority is included in the decisional memo and represents FDA's final benefit-risk determination for the application.<sup>13</sup>

In March 2015, CDER began a phased implementation of the revised templates in new drug reviews, beginning with the reviews of NME NDAs and original BLAs submitted to the Agency after March 1, 2015. BRFs completed as part of this rollout began appearing in the publicly posted review documentation for approved products near the end of calendar year 2015.

In August 2017, CDER further updated the review and decision templates, incorporating feedback from review staff and a requirement set forth in the Cures Act.<sup>14</sup> At that time, CDER expanded implementation of the revised templates for use in new drug review for all original 505(b)(1) NDAs and original 351(a) BLAs original NDAs, 505(b)(2) NDAs that include a new adequate and well-controlled clinical trial, and many types of efficacy supplements.<sup>15</sup> BRFs completed as part of this template rollout began appearing in the publicly posted review documentation for approved products in January 2018.

CBER is also updating and revising its process so that the BLA Clinical Review Memorandum captures patient experience data and related information required in the Cures Act<sup>16</sup>.

### **c. Train review and management staff on the revised templates and manuals**

Since March 2015, CDER's phased implementation of the BRF in clinical review and management templates has been accompanied by: a) an internal website containing the templates, background on the BRF, and supplementary materials; b) training on use of the new templates, offered bimonthly; c)

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<sup>12</sup> The BRIC serves the advisory, oversight, and support functions as outlined for the "Change Control Board" and "Benefit-Risk Advisory Group" in the 2013 Implementation Plan. CBER participates in the BRIC to foster cross-Center understanding and implementation.

<sup>13</sup> This standard process has been adapted in some cases to apply to a single, integrated review document to which members of the review team contribute to the review team collaborative. In this model, one person, typically the Cross-Discipline Team Lead (CDTL) completes the Benefit-Risk Framework.

<sup>14</sup> Under the Cures Act, FDA is required to "make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of the application." Thus, the revised primary clinical review template incorporates a section on Patient Experience Data to include this statement.

<sup>15</sup> Templates including a BRF are generally not applicable for supplements that do not contain a new adequate and well-controlled trial, such as CBE-0 labeling supplement and CMC manufacturing supplements.

<sup>16</sup> See footnote 14.

training and individual coaching by technical writing experts; and d) additional individual support to reviewers as needed.

Starting in 2014, CBER's Office of Biostatistics and Epidemiology added training materials on BRF into three annual training and courses: "Introduction to risk assessment for biologics," "Introduction to risk management for biologics," and "Introduction to risk communication for biologics." These courses offer training to CBER review staff on the fundamental principles of benefit-risk assessment, FDA's BRF, potential tools to support more quantitative benefit-risk assessment tools (such as value trees, forest plots, and multi-criteria decision analysis), and available resources to assist benefit-risk review of biological products.

**d. Develop an evaluation plan to ascertain the impact of the Benefit-Risk Framework in the human drug review process**

The 2013 Plan included a plan to assess the impact of the BRF in the human drug review process. In September 2015, FDA awarded a contract to a qualified third party to support an evaluation of the implementation of the BRF into CDER's and CBER's new drug review, in accordance with the 2013 Plan. In FY 2017, the contractor completed their evaluation and provided a final report based on their analysis and assessment. This evaluation is discussed in more detail in Section IV.

**e. Conduct two public workshops on benefit-risk considerations from the regulator's perspective**

In PDUFA V, FDA committed to holding two public workshops on benefit-risk considerations from the regulator's perspective. In 2014, FDA and Institute of Medicine<sup>17</sup> (now called the National Academies of Science, Engineering, and Medicine (NASEM)) convened a two-day workshop on *Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products*. This meeting brought together experts in drug development, regulatory science, and decision science to identify and discuss potential approaches to addressing the uncertainty inherent in complex drug review decisions. The workshop report, developed by NASEM, which includes the agenda, participants, and workshop summary, is available on the [NASEM website](#).

In FY 2017, FDA held the second of two public workshops on Benefit-Risk. This one-day meeting included presentations and panel discussion focused on: regulatory and industry experiences with approaches to structured benefit-risk assessments, approaches to incorporating patient perspectives into structured benefit-risk assessment, and exploration of methods to advance structured benefit-risk assessment. Information about this meeting, including the presentation slides, is available on [FDA's website](#).<sup>18</sup>

**f. FDA's Patient-Focused Drug Development initiative**

FDA recognizes the importance of enabling meaningful patient input in helping to inform the context for drug development and regulatory decision-making, including FDA's benefit-risk assessment. In PDUFA V, through the Patient-Focused Drug Development (PFDD) initiative, FDA began developing a more

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<sup>17</sup> This meeting was planned by an ad hoc planning committee identified and managed by NASEM. See <https://www.nap.edu/catalog/18870/characterizing-and-communicating-uncertainty-in-the-assessment-of-benefits-and-risks-of-pharmaceutical-products>

<sup>18</sup> See: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm378861.htm>

systematic way of gathering patients' perspectives on their conditions and currently available treatments. In FY 2013, FDA initiated a process to identify the set of disease areas to be addressed in the public meetings<sup>19</sup> and convened a series of consultation meetings with patient stakeholders to gather input into the format and structure of the public meetings. FDA conducted the first PFDD meeting in April 2013 concerning Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. By the end of FY 2017, FDA convened 24 meetings under the PFDD initiative, exceeding the PDUFA V commitment to hold 20 meetings. Information about each meeting is available on [FDA's website](#).<sup>20</sup>

Each FDA meeting resulted in a *Voice of the Patient* report that captures patient input from the public meeting, meeting webcast, and accompanying public docket. FDA carefully considers this input as we fulfill our regulatory role, including when advising sponsors about their drug development programs and when assessing products under review for marketing approval. This patient input can also support FDA's benefit-risk assessments. For example, most *Voice of the Patient* reports contain in an appendix a sample of the top two rows of the BRF table, drawing on various sources, including the input generated by the meeting. These samples represent the kind of information that FDA anticipates could be included in a BRF completed for a product under review that is indicated for the relevant condition.

FDA acknowledges that there are many more disease areas than could have been addressed in the FDA meetings conducted under PDUFA V. In 2016, to help expand the benefits of FDA's PFDD initiative, FDA began to welcome externally-led identification and organization of patient-focused collaborations to generate patient input in other disease areas, using the process established through FDA's PFDD as a model. As of December 31, 2017, nine externally-led meetings have been conducted by patient stakeholders for a variety of disease areas. Information about externally-led PFDD meetings and other resources can be found on [CDER's Patient-Focused Drug Development](#) webpage.<sup>21</sup>

The PFDD initiative undertaken in PDUFA V is an important step to help address the need to better enable patients to provide meaningful input into drug development. FDA recognizes the need to engage the wider stakeholder community and provide guidance on approaches to bridge from these PFDD meetings to more systematic, methodologically-sound approaches to collect patient input so that it becomes data that can further inform regulatory decision making. In December 2016, under Title III of the Cures Act, Congress directed FDA to take steps, including issuance of new guidance, to ensure that patient input is incorporated into drug development and can inform FDA's regulatory decision-making. In June 2017, as a first step toward implementation of these statutory requirements, FDA issued the [Plan for Issuance of Patient-Focused Drug Development Guidance](#). FDA's commitments under the 2017 FDA Reauthorization Act (FDARA) Title I (PDUFA VI)<sup>22</sup> also include commitments to enhance the new drug review program by enhancing the incorporation of the patient's voice in drug development and decision-making, through a series of efforts including the issuance of a series of new guidance closely aligned with provisions of the Cures Act.

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<sup>19</sup> In accordance with our commitments in PDUFA V, FDA engaged in a public process to identify the disease areas. In FY 2012, FDA published a Federal Register notice with a list of preliminary disease areas nominations for potential meeting focus during FY 2013–2015 and collected public input on these disease area nominations. In FY 2015, FDA conducted a similar process to identify the disease areas to be addressed during fiscal years (FYs) 2016–2017.

<sup>20</sup> See: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm>

<sup>21</sup> See: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm>

<sup>22</sup> See Section J.1 in the PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022: <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>



#### g. Other activities

In March 2015, the International Conference on Harmonization (ICH) identified an opportunity to update its guidelines document *M4E: The Common Technical Document (CTD) -- Efficacy* with enhanced guidance to drug applicants about the presentation of benefit-risk assessment information in their premarket regulatory submissions. FDA provided leadership on the ICH M4E(R2) Expert Working Group, which finalized revised guidelines in June 2016. M4E(R2) revises the M4E guidelines to include greater specificity on the recommended format and structure of applicants' benefit-risk assessments located in the CTD Section 2.5.6. In July 2017, FDA published guidance to industry entitled *M4E(R2): The CTD – Efficacy Guidance for Industry*, which integrates the ICH guidelines on presenting benefit-risk information in an applicant's submission.

During PDUFA V, CBER's Office of Biostatistics and Epidemiology also started to explore quantitative benefit-risk assessment approaches to help inform regulatory decisions in some specific product reviews.

During PDUFA V, FDA also engaged in dialogue with international regulators, pharmaceutical industry stakeholders, researchers, healthcare and patient stakeholders, and others regarding benefit-risk assessment to support drug development and regulatory decision-making.

### IV. Summary of Third-Party Evaluation conducted in PDUFA V

In September 2015, FDA awarded a contract to Eastern Research Group, Inc. to conduct an evaluation of the BRF implementation into CDER's and CBER's new drug review, in accordance with the 2013 Plan.<sup>23</sup> This evaluation was intended to assess the degree to which the use of the BRF provides utility to reviewer deliberations and communications of benefit-risk considerations; and to assess the degree to which the BRF provides a clear explanation of FDA approval decisions to public stakeholders, including patients, healthcare professionals, and applicants. The contractor, with oversight by an FDA Technical Advisory Group, conducted a multi-modal assessment involving: an independent review by the contractor of review processes and documentation; interviews with FDA staff; interviews with applicants whose product received approval; and interviews with external stakeholders such as patients, healthcare providers, and patient organizations. The evaluation cohort comprised NME NDAs and original BLAs that were received by FDA between March 1, 2015 and February 29, 2016 and received an approval or complete response action by May 17, 2017.

In September 2017, the contractor completed data collection on a cohort of 43 applications and provided FDA with a final report based on their analysis and assessment. This included a review of 142 documents, and individual or group interviews with: 104 FDA staff<sup>24</sup>; 45 representatives of drug applicants; and 154 external stakeholders.

The contractor presented their findings into several key areas:

- **BRF Integration into the new drug review process:** Overall, 87% of relevant review documents covered in the assessment cohort contained a BRF, with BRF inclusion being nearly universal in

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<sup>23</sup> A summary of this evaluation was presented by the contractor at FDA's September 18 public meeting.

<sup>24</sup> FDA staff included: Medical officers, primary clinical reviewers, Cross-Discipline Team Leaders, Division Directors, and Office Directors (signatory authorities for NMEs and original BLAs).

the reviews completed later in the assessment cohort. FDA staff opinions about including the BRF into the review process were mixed, but most staff saw some value. Seventy-five percent (75%) of FDA staff interviewed stated that the BRF has some value in (1) organizing and documenting their thinking about benefit-risk or (2) documenting a concise view of the review and recommendation. Twenty-five percent (25%) of FDA staff interviewed believed that the BRF is primarily used to communicate benefit-risk assessment externally. Most review staff agreed that the basic BRF format is effective and that there is value in making the effort to create the BRF in the established form. The contractor noted variability in the lengths of completed BRFs, types of content presented, and in approaches to presenting content.

- **BRF Alignment with Review Content:** Per feedback from FDA staff interviewed, the contractor found that in the assessment cohort, the content of the BRFs cohort aligned well with content found in their more detailed reviews. The contractor also found that the content of the primary clinical review BRFs aligned well with the content in a mock-up BRFs developed by an internal FDA Subject Matter Expert (SME) who was blinded to the original BRF and created the mock-up BRF based solely on information found in the detailed review.
- **Clarity and Understandability of BRF Content:** In interviews, the contractor asked FDA staff, applicants, and other external stakeholders to rate the clarity and understandability<sup>25</sup> of the completed BRFs. Mean ratings<sup>26</sup> for clarity and understandability ranged from “good” to “excellent” for each group. Most applicant and external stakeholder interviewees indicated that the BRFs were suitable for motivated readers who have at least some background with the therapeutic area. Most also agreed that the format of the BRF is effective in organizing and presenting content and helps makes content usable. Interviewees were mixed in their assessment of the value in having multiple versions of the BRF completed for each application. Interviewees who favored multiple versions appreciated the transparency of individual opinion. Interviewees with less favorable view of this approach thought that multiple versions introduced redundancy and might cause confusion among external audiences.
- **Usefulness of BRF Content:** In interviews, the contractor asked FDA review staff, applicants, and other external stakeholders to rate the usefulness of completed BRFs and to describe actual or anticipated uses. Mean usefulness ratings ranged from “good” to “excellent”. Applicants and other external stakeholders interviewed suggested ways to improve the usefulness of the BRF. Common suggestions included: publish the BRF as an easy-to-find standalone item, develop BRFs for more types of applications, such as efficacy supplements; and include information about patient perspectives, clinical trials, clinical considerations, and review dilemmas. Applicants stated that they would also like to (privately) receive BRFs for their applications that receive a complete response.<sup>27</sup> External stakeholders also expressed interest in having BRFs for products that are not approved made public.<sup>28</sup>

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<sup>25</sup> The contractor defined “clarity” as the extent to which the reader can follow the logic underlying the regulatory decision and key points are stated explicitly and are grouped and sequenced logically. The contractor defined “understandability” as the extent to which readers can follow key messages and simplest words and sentence structures are used.

<sup>26</sup> Rating categories included “excellent”, “good”, “fair”, and “poor”.

<sup>27</sup> FDA sends an applicant a complete response letter to indicate that the review cycle for an application is complete and that the application is not ready for approval.

<sup>28</sup> FDA does not currently publish information about applications that are not approved.

- **Usefulness of Training, Coaching, and Internal Review in Implementing the BRF:** The contractor found that awareness and use of staff support resources, while initially mixed, was high by the end of the assessment period. Many FDA staff interviewed stated that training and instructions have been helpful, especially for newer reviewers. They identified opportunities to enhance internal supports, for example, by providing more examples that address a range of typical review issues.

The contractor's final recommendations reflected the key findings from their evaluation. They stated that no major changes to the BRF were needed, but that minor enhancements could improve the consistency of the BRF content, the usability of the BRF from a technical perspective, and the usefulness of the BRF for external audiences. FDA has considered the contractor's findings and recommendations in the development of this implementation plan.

## **V. PDUFA VI Commitments on Enhancing Benefit-Risk Assessment**

During implementation of the PDUFA VI commitments, FDA will further the Agency's implementation of structured benefit-risk assessment, including incorporating the patient's voice in drug development and decision-making in the human drug review program. This section describes how FDA's plans to fulfill the commitments outlined in PDUFA VI.

### **a. Continue implementation of the Benefit-Risk Framework**

FDA's incorporation of the BRF into the review documentation processes and templates for new drug review will continue throughout the PDUFA VI reauthorization period. This includes use of the BRF application types that were included in CDER's expanded implementation of the templates in September 2017 (described in Section III.b). CDER and CBER will monitor for any challenges and adjust our implementation accordingly, with oversight by the BRIC and respective Center leadership. In PDUFA VI, FDA will also explore ways to enhance use of the BRF as an internal review tool earlier in the NDA/BLA review process.

The BRF was developed to be flexible in supporting FDA's decision making along the human drug lifecycle, including in the postmarket setting. During PDUFA V, FDA explored opportunities to apply the BRF to support internal discussions on complex postmarket benefit-risk assessments. In PDUFA VI, FDA plans to continue to explore more systematic use of the BRF in postmarket review.

Leveraging the key learnings from the implementation of the BRF during PDUFA V, including the recommendations from the third-party evaluation, FDA will seek to enhance the clarity and consistency of completed BRFs. This may include refining templates and guidelines to promote standard formatting and enhanced clarity in presentation of complex information.

Effective training and internal support is critical to the success of continued implementation of the BRF into the drug review process. FDA will continue to offer training and other resources to review staff on the fundamental concepts of benefit-risk assessment, the Benefit-Risk Framework, and its use to support drug review. Over time, FDA plans to continue building an internal repository of examples of BRFs as a reference for reviewers.

## **b. Participate in stakeholder meeting on benefit-risk assessment**

Input from stakeholders on their experiences and perspectives regarding FDA's benefit-risk assessment is important to help FDA ensure that we are effectively communicating the assessments and judgments that underlie our drug regulatory decisions. By the end of FY 2019, FDA will convene and/or participate in, at least one meeting, conducted through a qualified third party, to gather industry, patient, researcher, and other stakeholder input on applying the BRF throughout the human drug lifecycle and best approaches to communicating FDA's benefit-risk assessment. Input from this meeting will support development of the draft guidance on benefit-risk assessment for new drugs and biologics. Anticipated topics include those specified for coverage in the draft guidance outlined in the next section. Additional topics may be identified.

## **c. Draft guidance on benefit-risk assessment for new drugs and biologics**

In FY 2020, FDA will publish a draft guidance on benefit-risk assessment for new drugs and biologics. It is anticipated that this draft guidance document, when finalized, will provide drug sponsors and other stakeholders with a clearer understanding of how considerations on a drug's benefits versus risks factor into FDA's regulatory decisions throughout the drug development life-cycle, including premarket and postmarket phases. Industry stakeholders have indicated that having a clearer understanding of FDA's thinking can help inform a sponsor's internal decision-making about their drug development programs, particularly early in the product development. This information may also help patient stakeholders, researchers, and others gain insight into the unique regulatory framing of drug development.

As outlined in the PDUFA VI Commitment Letter, this draft guidance will:

- Articulate FDA's decision-making context and framework for benefit-risk assessment, illustrating the application of the benefit-risk framework throughout the human drug lifecycle, using a case study approach, if appropriate.
- Discuss appropriate interactions between a sponsor and FDA during drug development to understand the therapeutic context (i.e., the severity of disease that represents the targeted indication and the extent of unmet medical need in the target population) for regulatory decisions for the product at the various stages of drug development and evaluation.
- Discuss appropriate approaches to communicate to the public FDA's thinking on a product's benefit-risk assessment, such as through product-specific discussions using the BRF at FDA's advisory committee meetings.

Additionally, this guidance will discuss how relevant patient experience data and related information may be used to inform benefit-risk assessment, in accordance with the Cures Act.<sup>29</sup> In compliance with the timeline specified in the Cures Act, FDA intends to issue draft guidance by the end of June 2020 and intends to issue final guidance 18 months after the close of public comments on the draft guidance.

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<sup>29</sup> See Section 3002 of the 21<sup>st</sup> Century Cures Act: *(8) how the Secretary, if appropriate, anticipates using relevant patient experience data and related information, including with respect the structured risk-benefit assessment framework described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)) to inform regulatory decision making.*

#### **d. Revise relevant MAPPs and SOPPs**

Both CDER and CBER will continue to revise current procedural documents for staff and decision makers to include new approaches that incorporate FDA's benefit-risk framework into the human drug review program. This includes revision of the MAPPs that govern CDER's clinical review documentation processes and template, as well as the SOPPs document that governs CBER's clinical review documentation processes and templates.

#### **e. Conduct second evaluation of the Benefit-Risk Framework**

The first evaluation of FDA's implementation of the BRF (discussed in Section IV) provided FDA with valuable information affirming the utility of the BRF to internal and external stakeholders and identifying opportunities to improve upon the BRF and its implementation into new drug review. In FY 2021, FDA will conduct a second evaluation of the implementation of the BRF in FDA human drug review, using the PDUFA V evaluation as a baseline. As specified in the PDUFA VI commitment, this evaluation will also assess how reviewers across the organization apply the BRF and identify best practices and improvement needed in use of the BRF. Other objectives for the evaluation may also be identified. FDA will identify a qualified third-party to conduct the evaluation.

### **VI. Additional Opportunities to Enhance FDA's Benefit-Risk Assessment**

In addition to our commitments made in PDUFA VI and our relevant requirements specified in the Cures Act, FDA has identified other opportunities to continue to enhance FDA's benefit-risk assessment and communication in human drug review.

#### **a. Improving accessibility of Benefit-Risk Frameworks for approved products**

Currently, FDA's completed BRF for approved products are made public as part of applications' review documentation, which for CDER products is posted to Drugs@FDA, and for CBER's products is posted to Approvals and Clearances at [www.fda.gov/BiologicsBloodVaccines](http://www.fda.gov/BiologicsBloodVaccines) following approval. Input provided during the third-party evaluation suggests that it may be difficult for patients and healthcare providers to readily locate BRFs through this mechanism. During PDUFA VI, FDA will explore additional opportunities to improve the accessibility of BRFs for approved products to the public.

#### **b. Use of Benefit-Risk Frameworks to support Advisory Committee meetings**

FDA will explore opportunities to more systemically incorporate BRFs into product-specific discussions at advisory committee meetings. For example, development of a preliminary draft BRF in preparation for an advisory committee meeting may support development of the questions to the panel on topics related to benefit, risk, and benefit versus risk.

#### **c. Exploring additional tools to support benefit-risk assessment**

FDA's qualitative BRF serves as the foundational element of CDER's and CBER's structured benefit-risk assessment. With implementation of the BRF continuing to progress within FDA's drug review, the agency will continue to explore more systematic ways in which more structured or quantitative decision analysis approaches, methods, and tools can be used within the qualitative framework to inform

benefit-risk assessment for premarket or postmarket reviews, in cases where such approaches can provide unique value in supporting regulatory decision-making.

In October 2017, FDA participated in a meeting convened by Duke-Margolis Center for Health Policy<sup>30</sup> on advancing structured benefit-risk assessment in FDA's drug review. Participants included FDA regulatory decision makers and methodological experts, industry stakeholders, academic researchers, and health systems stakeholders. The meeting discussion focused on: 1) when and how 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 meeting provided useful insights, from a range of stakeholder perspectives, that can inform FDA's efforts to continue to advance approaches to support benefit-risk assessment.

## **VII. Conclusion**

Benefit-risk assessment is a fundamental element of FDA's drug regulatory decision-making. FDA and external stakeholders continue to see value in the Benefit-Risk Framework (BRF) as a tool to support FDA's internal decision making, improve communication to internal and external stakeholders, and improve transparency in the regulatory decision-making process. We look forward to enhancing the BRF and its implementation during PDUFA VI, as well as clarifying, through draft guidance, FDA's considerations on benefit-risk assessment throughout the drug development life-cycle, including premarket and postmarket phases. We also look forward to identifying opportunities to enhance the value of the BRF as a communication tool to drug developers, healthcare providers, patients, and others, and to explore potential additional tools that can be used within the qualitative BRF to further support FDA's benefit-risk assessments.

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<sup>30</sup> The Duke Margolis Center for Health Policy convened this meeting under a cooperative agreement with FDA. Information on this meeting is available at <https://healthpolicy.duke.edu/events/advancing-structured-benefit-risk-assessment-fda-review>.