

Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document May 3, 2019

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I. Introduction

In accordance with commitments established in the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) in 2017,¹ the FDA intends to publish draft guidance in 2020 on benefit-risk assessment for new drugs and biologics (referred to collectively in this document as drugs). The planned guidance will articulate the approach of FDA’s Center for Drug Evaluation and Research (CDER) and FDA’s Center for Biologics Evaluation and Research (CBER) to conducting the benefit-risk assessments that guide drug regulatory decision-making.² It will discuss opportunities for FDA and sponsors to effectively discuss benefit-risk considerations throughout the drug development lifecycle. It will also discuss how benefit-risk information may effectively be communicated to the public. To meet requirements established in the 21st Century Cures Act,³ the planned guidance will also discuss how relevant patient experience data may be used to inform benefit-risk assessments. Further information on FDA’s commitments are found in the 2018 PDUFA VI implementation plan entitled “[Benefit-Risk Assessment in Drug Regulatory Decision-Making.](#)”

The intent of the planned benefit-risk guidance is to provide drug sponsors and other stakeholders with better clarity about how considerations about a drug’s benefits, risks, and risk management factor into FDA’s regulatory decisions about its marketing authorization. Industry stakeholders have indicated that having a clearer understanding of FDA’s assessments can help inform sponsors’ decisions about their drug development programs and the evidence they generate in support of their new drug application (NDA) or biologics license application (BLA). It may also help patients and other stakeholders gain further insight into the regulatory framing of drug development and evaluation.

On May 16, 2019, the Duke-Margolis Center for Health Policy will convene a public meeting, on behalf of FDA, entitled “Characterizing FDA’s Approach to Benefit-Risk Assessment Throughout the Medical Product Life Cycle.” The stakeholder input obtained from this meeting will inform development of the draft guidance. Information on the public meeting is found at healthpolicy.duke.edu/events/. The public is encouraged to contribute input through participation at the meeting and through the public docket.⁴

This document provides background information on FDA’s approach to benefit-risk assessment for drugs, including key considerations for the benefit-risk assessments that support FDA’s regulatory decisions about the marketing authorization of a drug. It is intended to support discussion at the public meeting on: (i) how evidence generated by sponsors during drug development can best inform the benefit-risk assessment of a marketing application; (ii) how benefit and risk information can be effectively communicated to support benefit-risk assessments; and (iii) how benefit-risk assessment informs FDA and sponsor decision-making in the postmarket setting.

II. FDA's Approach to Benefit-Risk Assessment of Drugs and Biologics

Broadly speaking, *benefit-risk assessment* in FDA's drug regulatory context is making a judgment as to whether the expected benefits (with their uncertainties) of the drug outweigh the potential risks (with their uncertainties and approaches to manage risks) associated with its expected use.

Benefit-risk assessment along a product's life cycle – from development through approval and into the postmarket setting – can take several forms, for different purposes. FDA's planned benefit-risk guidance will focus on the benefit-risk assessments that support FDA's regulatory decisions about the marketing authorization of a drug. Regulatory decisions made regarding the authorization include premarket approval of a new drug application and any regulatory requirements for approval, such as inclusion of a boxed warning in the Full Prescribing Information, postmarket studies, or risk evaluation and mitigation strategies (REMS).⁵ It also includes regulatory decisions about the product's marketing after a product is approved. It is important to note, however, there are many regulatory decisions other than marketing authorization that must consider the benefits and risks of a product for its expected use. For example, before an investigational drug can be administered in first-in-human clinical trials, FDA must determine that the product will not pose unreasonable risks to the participants. Other examples of regulatory decisions with benefit and risk considerations are expanded access⁶ and emergency use authorizations.⁷

In the context of the marketing authorization of a drug, FDA's regulatory decision-making is based on a determination that the drug is effective and that its expected benefits outweigh its potential risks to patients and to public health. FDA's decision-making is guided by its regulatory framework, statutes, as well as its precedents and policies, which are often expressed through FDA's issued guidance. For example, the standards for establishing a drug's effectiveness as a requirement for approval are codified in the Code of Federal Regulations;⁸ the typical standard for approval has been interpreted as requiring evidence from two adequate and well-controlled clinical trials.⁹ However, applicable statutes and implementing regulations also give FDA, in appropriate circumstances, regulatory flexibility in the type and quantity of evidence required to establish effectiveness.¹⁰

Within the legal and policy framework, FDA's decisions regarding the marketing of a particular drug require a case-specific assessment of science and medicine, which considers:

- **The therapeutic context** in which the product will be used, including the nature and severity of the condition the drug is intended to treat or prevent, and how well patients' needs are being met by currently available treatments.
- **The evidence** submitted in the premarket application and/or generated in the postmarket setting. Example of evidence include clinical data, nonclinical data, patient experience data, product quality information, spontaneous reports of adverse events, and real-world data.
- **Uncertainties** about the product's benefits and risks to patients. The body of evidence is inevitably incomplete, thus creating the need for scientific and regulatory judgment to determine whether the product's benefits outweigh the risks despite this uncertainty, and whether additional measures are needed to address this uncertainty.

- **FDA’s regulatory options** to address uncertainties and manage risks, for example through the requirement of additional clinical trials, additional product quality information, safety labeling, and REMS.
- **Values of and tradeoffs between benefits and risks**, within the therapeutic context. Regulatory judgments consider what is important to patients as well as what is important to public health.

FDA’s benefit-risk assessment is the process by which FDA integrates the above factors to inform regulatory decisions. FDA’s vehicle for conducting these assessments is the Benefit-Risk Framework for Human Drug Review.¹¹ The Benefit-Risk Framework (Figure 1) provides a structured, qualitative approach and guiding questions for identifying, assessing, and drawing conclusions on the key considerations that factor into the benefit-risk assessment:

- The rows outline the key dimensions of the assessment including *Analysis of Condition* and *Current Treatment Options* (these two rows form the *therapeutic context*), as well as the product-specific assessments of *Benefit* and *Risk and Risk Management*.
- The columns distinguish two key inputs to each dimension: the *Evidence and Uncertainties* that are most pertinent to the benefit-risk assessment and the *Conclusions and Reasons* on the strength of evidence and potential significance of the findings or review issues.
- Finally, the *Conclusions Regarding Benefit-Risk* integrates the dimensions and considers how evidence and uncertainties about a drug’s benefits and risks are weighed in the context of the severity of the condition and the patients’ current unmet needs.

Figure 1. FDA’s 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		

At the May 16 public meeting, FDA will discuss in more detail the specific considerations that factor into each dimension of the Benefit-Risk Framework, as well as how considerations on these dimensions are integrated to reach conclusions regarding benefit-risk. Table 1 provides an overview of those considerations. For example, when assessing the expected benefits of the drug, FDA considers the strengths and limitations of trial design; the clinical relevance of the study endpoints as measures of clinical outcomes of importance to patients; the clinical significance of the demonstrated results; the ability to predict which patients may benefit; the ability of individual patients to determine whether they are gaining benefit from the drug; and the generalizability of the benefits demonstrated in the trial to the postmarket setting. FDA welcomes input on these and other considerations.

Table 1 also highlights common sources of uncertainty that can have implications for benefit-risk assessment. Some uncertainties can be anticipated based on the trial design or product design, such as the uncertainty associated with choice of control group, study duration, definition of study endpoints, exclusion criteria, data quality assurance, and manufacturing process controls. Other uncertainties become apparent only after the trial evidence has been generated, such as uncertainty about significance of an unexpected safety signal.

Table 1: Key Considerations for FDA’s premarket benefit-risk assessment of new drug applications

BRF Section	Key Considerations	Common Sources of Uncertainty
Analysis of Condition	<ul style="list-style-type: none"> • Context of use for proposed indication: intended medical use, target patient population • Relevant clinical aspects of the condition • Patient-focused disease burden 	<ul style="list-style-type: none"> • Ability to define target population • Complexity of disease (e.g., effect on understanding drug’s mechanism of action) • Extent of patient input on disease burden
Current Treatment Options	<ul style="list-style-type: none"> • Goals of current standard of care • Efficacy and safety of available therapies • Burden of treatment (e.g., administration) • Aspects of disease burden not addressed by current therapies 	<ul style="list-style-type: none"> • Patient utilization of treatments • Extent of evidence about therapies not FDA-approved for the indication • Extent of patient input on unmet needs
Benefit	<ul style="list-style-type: none"> • Strengths/limitations of clinical trial: potential implications for assessing drug efficacy • Clinical relevance of the study endpoints: ability to measure or predict clinical outcomes of importance to patients • Demonstrated results and their clinical significance, informed by: <ul style="list-style-type: none"> ○ Magnitude, duration of treatment effects ○ Nature of benefit (e.g., disease modifying, symptom reduction) ○ Distribution of effects in the study population ○ Potential effect on future clinical outcomes (e.g., death, organ damage) ○ Ability to predict which patients may benefit ○ Ability for patient/provider to assess individual benefit ○ Patient perspectives on benefit • Generalizability of the clinical trial evidence to the to-be-marketed patient population in the postmarket setting 	<ul style="list-style-type: none"> • Program or trial design; e.g., less than two randomized controlled trials, use of single arm-designs, use of observational data • Statistical uncertainty • Relationship between study endpoint and clinical outcomes • Extent of patient input on the significance of expected benefits • Populations not included or underrepresented in clinical trials • Quality and integrity of data

BRF Section	Key Considerations	Common Sources of Uncertainty
Risk and Risk Management	<ul style="list-style-type: none"> • Strengths/limitations of safety evaluation: potential implications on assessing drug risks • Serious adverse events or safety signals—clinical significance and remaining uncertainties, considering: <ul style="list-style-type: none"> ○ Magnitude, duration, severity of harms ○ Reversibility of harm (e.g., upon cessation of treatment) ○ Distribution of harms in the study population ○ Potential effect on future clinical outcomes (e.g., death, organ damage) ○ Ability to predict which patients may be at risk ○ Ability to prevent, detect, and mitigate harms ○ Patient perspectives on risks • Adverse effects (e.g., nausea) that could affect tolerability or adherence • Potential impact of product quality or device issues on effectiveness or safety • Additional safety issues considering how prescribers and real-world use in the postmarket setting may differ from the clinical trial setting • Effectiveness of strategies to manage risks 	<ul style="list-style-type: none"> • Size of safety population; background rate of adverse event in the treated population (e.g., trials may be underpowered to identify all safety risks) • Understanding of the relationship between safety endpoints and clinical outcomes • Potentially susceptible patient groups (e.g., elderly, patients with co-morbidities) not included or underrepresented in clinical trials • Quality and integrity of data • Challenges or barriers to quality health care delivery • Untested risk management strategies • Potential differences between the development batch of the drug versus commercial scale
Conclusions Regarding Benefit-Risk	<ul style="list-style-type: none"> • How therapeutic context affects threshold for benefits and tolerance for risk and uncertainty <ul style="list-style-type: none"> ○ Benefit and risk values and tradeoffs, including patient perspectives ○ How the product, if approved, may enhance the treatment armamentarium • Importance of unresolved uncertainties • Need for labeling (e.g., boxed warning) or REMS to support favorable benefit-risk assessment • Need for postmarketing evidence to address uncertainty 	<ul style="list-style-type: none"> • Extent of patient and other input on benefit and risk values and tradeoffs • Ability to generate the desired evidence of safety or benefit (e.g., through randomized control trials or observational studies) in the postmarket setting

Aspects of the therapeutic context affect FDA’s tolerance for uncertainty and the tradeoffs about a product’s benefits and risks. For example, in the case of accelerated approval, FDA may accept an effect on a surrogate endpoint that is reasonably likely to predict benefit, rather than requiring a validated surrogate or direct measure of clinical outcomes, if the drug is expected to provide a meaningful advantage over available therapies in the treatment of a serious or life-threatening condition.¹² Similarly, FDA’s determination that serious toxicities may be acceptable for an oncology drug, provided adequate benefit is established, is influenced by the life-threatening nature of the condition and the familiarity of oncologists with the risks of treatment and the management of these risks. Regulatory decisions regarding vaccines, however, must consider that the target population may be millions of healthy people, often children, in order to prevent disease; this illustrates how important the context is when assessing the tolerance for potential risk associated with such products.

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. As part of the [Patient-Focused Drug Development](#) and Science of Patient Input¹³ initiatives, FDA is working to advance the development and use of systematic approaches to better incorporate the patient’s voice

into drug development and evaluation. In the planned benefit-risk guidance, FDA intends to include discussion on how patient experience data, including patient input on disease burdens, meaningful outcomes, and potential benefit-risk tradeoffs, can inform benefit-risk assessment. FDA may also include discussion on when this information can be generated to best inform those assessments. This discussion will complement the [series of methodological guidances](#) that FDA is developing on the collection of patient experience data and the use of such data and related information in drug development.

FDA’s benefit-risk assessment fundamentally involves a qualitative judgment about whether the expected benefits of a product outweigh its potential risks. For many regulatory decisions, the supporting benefit-risk assessments can be sufficiently conducted and communicated through the Benefit-Risk Framework. Some decisions, however, involve complex or novel challenges in which uncertainties about the drug’s benefits, risks, or tradeoffs may not be fully addressed through a qualitative process. FDA continues to explore ways in which additional approaches and tools can supplement the Benefit-Risk Framework to further support drug development and evaluation, in cases where doing so adds value. FDA’s efforts have coincided with similar efforts by industry, researchers, patient stakeholders, and other regulators. Examples include approaches to better characterize uncertainty about the benefits or risks; approaches to incorporate information on benefits, risks, and values into quantitative benefit-risk analyses; and approaches to more systematically incorporate patient preference information to support assessment of the tradeoffs between benefits and risks.

III. Activities in Premarket Development that May Inform Benefit-Risk Assessment

Decisions and activities undertaken by sponsors in the development of their products, and the evidence generated to support their marketing applications, can have a significant impact on the ultimate benefit-risk assessments that support drug regulatory decision-making. Figure 2 presents a sample of activities that may have particular bearing on FDA’s benefit-risk assessments. It is important to note that these decisions and activities are also important in supporting any benefit-risk assessments the sponsor considers within their own development program.

Figure 2. Sample milestones along the drug lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization. Milestones may not apply to all drug development programs.

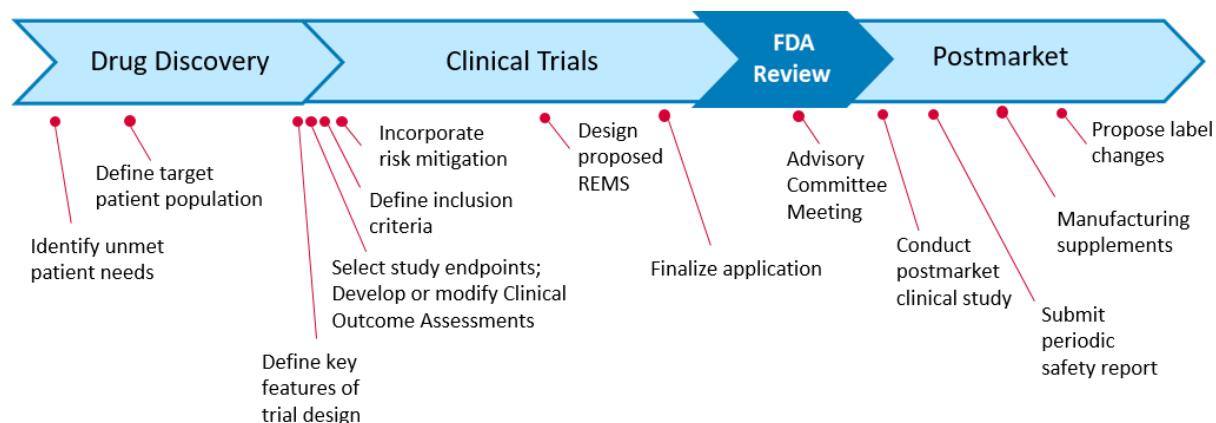


Table 2 illustrates how drug development activities can inform benefit-risk assessments. For example, the clinical relevance of study endpoints is a key consideration in FDA’s assessment of the drug’s benefit (Table 1). Gathering input from patients early in development can clarify specific areas of unmet patient need that a new treatment may seek to address. It can also help inform how to best measure treatment effects in clinical trials. At the public meeting, FDA is interested in discussion of these and other drug development activities that relate to FDA’s key considerations.

Table 2. Example of Linking Drug Development Activities to FDA’s Benefit-Risk Framework

Key consideration in FDA’s Benefit-Risk Framework (Table 1)	What development activity or evidence will likely inform FDA’s benefit-risk assessment (Figure 2)	What should sponsor consider when generating evidence?	What FDA guidance or other resources should be consulted?
Benefit: Clinical relevance of the study endpoints: ability to directly measure or predict clinical outcomes of importance to patients	Drug Discovery: Identifying unmet patient needs Clinical Trials: Selecting study endpoints; Developing or modifying Clinical Outcome Assessments	Collecting robust patient input on the symptoms or other aspects of their condition that matter most to them can inform and strengthen rationale for the selection of endpoints, development of COAs	FDA’s Patient-Focused Drug Development Guidance Series ^{14,15}

In the draft guidance, FDA also plans to discuss opportunities to enhance discussions between FDA and sponsors during drug development about key considerations for benefit-risk assessment. As shown in Figure 2, sponsor decisions made even early in drug development can affect the eventual benefit-risk assessment about the drug in the review of its marketing application; therefore, incorporating more purposeful discussion between FDA and sponsors on benefit-risk considerations may add value at several stages of drug development. FDA may also discuss when more formal (e.g., quantitative) benefit-risk analyses submitted by the sponsor may add value to the body of evidence the sponsor has generated.¹⁶ FDA welcomes input on these topics.

IV. Effectively Communicating Benefit-Risk Assessment Information

The effective communication of information by sponsors on the drug’s benefits, risks, tradeoffs and uncertainties is important to informing the benefit-risk assessments that support regulatory decision-making. A critical source of benefit-risk information is the sponsor’s NDA or BLA. The International Conference on Harmonization (ICH) guidelines *M4E(R2): The Common Technical Document (CTD) – Efficacy*, revised in 2016, provide recommendations on the presentation of benefit-risk assessment information in premarket applications (in Section 2.5.6 of the CTD). In July 2017, FDA adopted the ICH guidelines in its own guidance to industry entitled [M4E\(R2\): The CTD – Efficacy Guidance for Industry](#). FDA’s draft benefit-risk guidance aims to build on this guidance to discuss how sponsors can effectively present information about a product’s benefit-risk profile in marketing application submissions to FDA. FDA may also include discussion on how visual representations that compare key benefits and risks, such as the estimated absolute risk difference or number needed to treat/number needed to harm (NNT/NNH), may add value. However, these approaches can also be misleading if measures are not carefully defined and presented. FDA welcomes input on the considerations for including different types of presentations of benefit and risk information.

FDA also continues to explore ways to enhance the value of the Benefit-Risk Framework as a tool to communicate the Agency's current thinking on a product's benefit-risk assessment to sponsors and the public. The Benefit-Risk Framework has become an important tool to communicate in FDA's review documentation the benefit-risk assessments that informs the Agency's approval decision for an NDA or BLA.¹⁷ Another important mechanism for communicating benefit-risk information in support of regulatory decision-making—and more broadly, to the public—is the product-specific Advisory Committee meeting.¹⁸ For example, utilization of a preliminary draft Benefit-Risk Framework may support development of the questions to the Advisory Committee on topics related to benefit, risk, and benefit-risk assessment. FDA welcomes input on the potential to leverage the Benefit-Risk Framework to support advisory committee discussions.

V. Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Postmarket Setting

Benefit-risk assessment does not end with FDA's approval of a drug. In the postmarket setting, both sponsors and FDA continue to make decisions related to marketed drugs as information continues to be generated about the benefits and risks of that drug. The evidence used to inform these decisions, however, comes from a diverse set of sources. This information can be collected in a systematic way for specific purposes—such as for a postmarketing requirement or for REMS assessments—or it can be generated through surveillance and pharmacovigilance. For serious safety concerns identified in the premarket review, uncertainty about the risks may decrease over time, as the body of evidence (including from postmarketing clinical trials, studies, and surveillance) builds.

Many postmarketing decisions, such as modifications to a REMS program or updates to product labeling, consider benefit and risk, even if a formal assessment using the Benefit-Risk Framework is not performed. At times, however, a new safety concern emerges that requires a more formal benefit-risk assessment to inform postmarket regulatory decision-making. Examples of such decisions include marketing withdrawal, initiation or removal of a REMS, and inclusion or removal of a boxed warning. The benefit-risk assessments that guide these decisions consider the evolving therapeutic context, including availability of additional treatments, evidence and uncertainties from real-world use of the drug, and the potential impacts that regulatory actions have on healthcare providers' and patients' decision-making. In the draft guidance, FDA plans to articulate considerations for benefit-risk assessment that may be particularly significant to post-marketing regulatory decisions. FDA may also discuss how patient input collected in the post-marketing phase can inform benefit-risk assessment, and when more formal benefit-risk assessment approaches may add value in the postmarket setting.

The public meeting on benefit-risk will explore opportunities for sponsors and FDA to enhance discussion of benefit-risk considerations in the postmarket setting. Periodic safety reporting is an important mechanism for sponsors to communicate information that can inform FDA's benefit-risk assessment in postmarket review. For example, ICH Guidelines E2C(R2)¹⁹ published in 2012 and adopted as guidance by FDA in 2016,²⁰ provide recommendations on developing an optional Periodic Benefit-Risk Evaluation Report (PBRER) with the objective to “present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile (p.2).”

FDA is also exploring how to enhance the Benefit-Risk Framework as a tool to support these postmarket benefit-risk assessments. FDA welcomes input on how to utilize the framework in this context.

VI. Conclusions

Benefit-risk assessment is a fundamental element of FDA’s drug regulatory decision-making. We look forward to clarifying, through guidance, FDA’s considerations on the benefit-risk assessments that support decisions about marketing authorization and how those assessments can be shaped by evidence generated throughout the drug life cycle. We also look forward to identifying opportunities to enhance the value of the Benefit-Risk Framework as a communication tool to drug developers, healthcare providers, patients, and others, and to explore additional approaches that can be used within the qualitative Benefit-Risk Framework to further support benefit-risk assessments.

In compliance with the timeline specified in the 21st Century Cures Act, FDA intends to issue draft benefit-risk guidance by the end of June 2020 and final guidance 18 months after the close of public comments on the draft guidance. The guidance may address the range of topics covered in this discussion document and other relevant topics.

¹ 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>.

² The Center for Devices and Radiological Health (CDRH) has a similar framework for medical devices. See <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM506679.pdf>.

³ See Section 3002 of the 21st Century Cures Act.

⁴ <https://www.federalregister.gov/documents/2019/04/24/2019-08219/characterizing-the-food-and-drug-administrations-approach-to-benefit-risk-assessment-throughout-the>

⁵ More information on REMS is available at: <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems>.

⁶ For more information: <https://www.fda.gov/news-events/public-health-focus/expanded-access>.

⁷ For more information: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>.

⁸ FDA must determine “substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use.” (21CFR314.125, 21CFR314.126)

⁹ See FDA’s 1998 guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf>).

¹⁰ For example, FDA’s 2014 guidance for Industry on Expedited Programs for Serious Conditions – Drugs and Biologics articulates FDA’s interpretation of the flexibility codified in 21CFR314 subpart H, 21CFR601 subpart E. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

¹¹ Information on development of the Benefit-Risk Framework and its implementation in the drug review process is provided in FDA’s 2013 PDUFA V Implementation Plan “[Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making](#)” and FDA’s 2018 PDUFA VI Implementation Plan “[Benefit-Risk Assessment in Drug Regulatory Decision-Making](#).”

¹² See FDA’s 2014 guidance for Industry on Expedited Programs for Serious Conditions – Drugs and Biologics. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

¹³ <https://onlinelibrary.wiley.com/doi/full/10.1002/lrh2.10032>

¹⁴ <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm610442.pdf>

¹⁵ <https://www.fda.gov/drugs/newsevents/ucm607276.htm>

¹⁶ A detailed discussion on specific benefit-risk related methodologies, such as design and analysis approaches for patient-preference studies or multicriteria decision analyses is considered outside the scope of the planned guidance. Discussion on how information generated from such methods may be included in the FDA-approved labeling of marketed products is also considered outside the scope of the planned guidance.

¹⁷ Since 2013 for CBER and 2015 for CDER, Benefit-Risk Frameworks are included as part of the publicly-available review documentation for approved products and can be accessed at Drugs@FDA (<https://www.accessdata.fda.gov/scripts/cder/daf/>).

¹⁸ For more information, visit: <https://www.fda.gov/advisory-committees>.

¹⁹ See International Council on Harmonization Guidelines (2012) Periodic Benefit-Risk Evaluation Report E2C(R2), p. 2 https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf.

²⁰ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299513.pdf>