Benefit-Risk Assessment for New Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Graham Thompson, 301-796-5003, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The intent of this guidance is to clarify for drug[2] sponsors and other stakeholders how considerations about a drug's benefits, risks, and risk management options factor into certain premarket and postmarket regulatory decisions that the Food and Drug Administration (FDA or Agency) makes about new drug applications (NDAs) submitted under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as well as biologics license applications (BLAs) submitted under section 351(a) of the Public Health Service Act (PHS Act).[3] This guidance first articulates important considerations that factor into the Center for Drug Evaluation and Research's (CDER) and the Center for Biologics Evaluation and Research's (CBER) benefit-risk assessments, including how patient experience data[4] can be used to inform the benefit-risk assessment. It then discusses how sponsors can inform FDA's benefit-risk assessment through the design and conduct of a development program, as well as how they may

[1] This guidance has been prepared by the Office of Strategic Programs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, unless otherwise specified, all references to *drugs* include both human drugs and biological products other than drugs or biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[3] For the purposes of this guidance, *biologics license applications* and *BLAs* refer to BLAs submitted under 351(a) of the PHS Act (42 U.S.C 262(a)). BLAs submitted under section 351(k) of the PHS Act (i.e., applications for biosimilar or interchangeable biologics products) are outside the scope of this guidance.

[4] For the purposes of this guidance, the term *patient experience data* includes data that (1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers), and (2) are intended to provide information about patients' experiences with a disease or condition, including: (A) the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy on patients' lives; and (B) patient preferences with respect to treatment of such disease or condition. This definition is found in section 569C(c) of the FD&C Act, (codifed at 21 U.S.C. 360bbb-8c) and is referred to in section 3002 of the 21st Century Cures Act, which directed FDA to issue certain guidance documents regarding the collection of patient experience data (see section 3002(b) of the 21st Century Cures Act).

present benefit and risk information in the marketing application. It also discusses opportunities for interaction between FDA and sponsors to discuss benefit-risk considerations in connection with the development of an NDA or BLA. This guidance concludes with additional considerations on benefit-risk assessments that inform regulatory decision-making in the postmarket setting.

This guidance pertains to benefit-risk assessments made to support certain regulatory decisions about NDAs or BLAs, from premarket approval through the postmarket setting. This includes decisions regarding any regulatory requirements for approval, such as inclusion of a boxed warning in approved labeling, postmarketing study requirements and commitments, and risk evaluation and mitigation strategies (REMS).[5] These regulatory decisions are made in accordance with specific, applicable legal and regulatory authorities and criteria.[6] This guidance touches on some of these authorities but does not attempt to list or address them all.

This guidance does not directly address other regulatory decisions that may occur throughout the drug development lifecycle, such as decisions regarding first-in-human trials of an investigational new drug (IND) and expanded access applications,[7] which also may require FDA to consider information about the benefits and risks of an investigational or marketed drug for its proposed use. However, the concepts discussed in this guidance may be still relevant to these other types of decisions.

The Agency developed this guidance document in accordance with goals under associated with the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) under Title I of the FDA Reauthorization Act of 2017[8] and requirements under section 3002(c)(8) of the 21st Century Cures Act to issue guidance relating to using relevant patient experience data and related information to inform regulatory decision-making.[9] This guidance draws from, and is consistent with, the International Council for Harmonization's (ICH) guidance for industry *M4E(R2): The Common Technical Document (CTD)—Efficacy* (ICH M4E(R2)) (July 2017).[10]

[5] More information on REMS is available at FDA's Risk Evaluation and Mitigation Strategies REMS web page, available at https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

[6] See, e.g., sections 505-1 and 505(o)(3) of the FD&C Act (REMS and PMRs, respectively) and 21 CFR 201.57 (labeling).

[7] More information on expanded access is available at FDA's Expanded Access web page: https://www.fda.gov/news-events/public-health-focus/expanded-access.

[8] This guidance satisfies the goal under section I.J.2.c. of the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022 (goals letter) to publish a draft guidance on the benefit-risk assessment for new drugs and biological products, available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022.

[9] This guidance addresses a requirement in section 3002(c)(8) of the 21st Century Cures Act, available at https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

[10] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. FDA'S APPROACH TO THE BENEFIT-RISK ASSESSMENT OF NEW DRUGS AND BIOLOGICS

A. Regulatory Background

Under the FD&C Act, for a new drug to be approved for marketing in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[11] The demonstration of effectiveness under this standard requires substantial evidence that the drug will have the effect it purports or is represented to have.[12, 13] Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks.

Benefit-risk assessment is thus integrated into FDA's regulatory review of marketing applications for new drugs and biologics.[14] Broadly speaking, benefit-risk assessment in FDA's drug regulatory context is making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to

[11] See section 505(d) of the FD&C Act. Under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) licenses for biologics have been issued only upon a showing that the products are "safe, pure, and potent." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered "substantial evidence" of effectiveness to be necessary to support licensure.

[12] See Section 505 (d) of the FD&C Act (21 U.S.C. 355(d)). The "substantial evidence" standard refers to both the quality and the quantity of the evidence that the drug will have benefit. See the May 1999 guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. The Agency has also published a draft guidance for public comment on this topic entitled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[13] Biological products are subject to provisions in both the FD&C Act as well as the PHS Act. Biologics license applications have to meet applicable requirements in the PHS Act to ensure the continued safety, purity, and potency of the product (see 21 CFR parts 600, 601, and 610).

[14] Section 905 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), amends section 505(d) of the FD&C Act by requiring FDA to "implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for premarket approval of a drug."

managing risks) under the conditions of use described in the approved product labeling.[15] Benefit-risk assessment takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in an NDA or BLA, as well as many other factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.

The benefit-risk assessment for a new drug can be straightforward in cases when a drug's benefit is established as clinically meaningful and the drug's safety profile is well-characterized with no serious safety risks identified. The benefit-risk assessment becomes more challenging in cases where the potential for serious safety risks is identified or expected to exist, e.g., risks that are life-threatening or associated with significant morbidity. In such cases, making an informed judgment that a drug has a favorable benefit-risk profile requires determining that the drug's benefits and risks are sufficiently characterized and that the benefits to the indicated population will outweigh the safety risks if the product is approved. This determination requires a thorough assessment of the available evidence, recognition of the data gaps, and careful consideration of a complex set of factors, including the severity of the condition, the patient population, and the current treatment landscape.

In cases where serious risks are anticipated, certain findings may nevertheless weigh in favor of a favorable benefit-risk profile for the drug to support approval. For example, FDA may determine a drug has a favorable risk profile if it clearly demonstrates direct and meaningful benefit on the most important clinical outcomes for a serious or life-threatening disease or condition. Or, it may be determined that the drug represents a specific important advantage over currently available therapies (e.g., is effective in patients who do not respond to available therapies, or treats an important clinical outcome not addressed by current therapies). A favorable benefit-risk assessment may also require demonstrating that adequate measures can be implemented to keep risks to an acceptable level in the postmarket setting. Finally, in some cases, a favorable benefit-risk assessment can be established by identifying a subpopulation (e.g., characterized by disease severity, genetic, pathophysiologic or historical factors) for whom the benefits outweigh the risks even if they do not do so in a broader population, and then targeting the drug's labeled indication to that population. This may also apply to drugs that rapidly provide symptomatic relief or functional improvements to individual patients, such that patients who are not benefiting soon after starting the drugs can stop them and mitigate their individual risks.

At times, there may be a tension between the benefit-risk assessment that takes into account the intended patient population as a whole versus the individual assessment that a prescriber and patient may make considering a patient's specific circumstances and condition. For example, FDA may conclude that if a drug were to be approved, the expected frequency of serious adverse events in the population, if approved, would outweigh the benefits of the drug, even if some patients might be willing to accept such risks. This can occur, for example, when the benefit of a

[15] For purposes of this guidance, key benefits are favorable effects generally assessed by primary and other clinically important endpoints across the studies in a development program; key risks are unfavorable effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity and/or seriousness (see ICH M4E(R2)).

drug is modest, and prediction or mitigation of serious, irreversible adverse events is difficult. If it is possible to identify those individuals or subpopulations most likely to experience the greatest benefit, the least risk, or both, the benefit-risk assessment for the intended population is more likely to be found favorable and the individual decision-making by patients and their healthcare providers may be better informed.

In certain circumstances, such as in the review of drugs to diagnose and treat communicable diseases or drugs identified as controlled substances,[16] FDA's benefit-risk assessment incorporates broader public health considerations for both the target patient population and others, such as risks related to misuse, accidental exposure, or disease transmission.

FDA's benefit-risk assessment comprises a case-specific, multi-disciplinary assessment of science and medicine, which considers:

- **The therapeutic context** in which the drug will be used, including the nature and severity of the condition the drug is intended to prevent, treat, cure, mitigate, or diagnose, and how well patients' needs are being met by currently available treatments. Therapeutic context is particularly important in cases where it is necessary to determine whether a serious risk associated with the drug is outweighed by its demonstrated benefit; greater risk may be more acceptable if there are no available therapies or when a clear advantage over available therapies can be demonstrated, for example, by showing that the drug is effective in patients who do not respond to available treatments. FDA is likely to have a lower tolerance for potential serious risks or toxicities when a drug is intended to treat conditions for which many treatment options with lesser risks are available, or when it evaluates preventative medicines, where the target population may be healthy people.

- **The evidence** submitted in the premarket application and/or generated in the postmarket setting that informs FDA's understanding of the benefits and risks of the drug. Sources of evidence include clinical data, nonclinical data, patient experience data, product quality information, spontaneous reports of adverse events, and epidemiologic data.

- **The uncertainties** about the drug's benefits and risks. Although uncertainty can be reduced through careful study design and conduct, some uncertainty in the body of evidence available at the time of regulatory decision-making is inevitable, e.g., the frequency of rare serious adverse events or whether the drug's effectiveness persists in long-term use. With appropriate consideration of this uncertainty, the Agency uses

[16] For example, FDA's draft guidance for industry *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework* (June 2019), explains that, "because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA . . . considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others." When final, this guidance will represent the FDA's current thinking on this topic. Section 3001 of the SUPPORT for Patients and Communities Act (SUPPORT Act) (Public Law 115-271) recognizes that FDA may incorporate the risks of misuse and abuse of a controlled substance (as defined in section 102 of the Controlled Substances Act (21 U.S.C. 802)) into the benefit-risk assessments under subsections (d) and (e) of section 505 of the FD&C Act (21 U.S.C. 355), section 510(k) of the FD&C Act (21 U.S.C. 360(k)), or section 515(c) of the FD&C Act (21 U.S.C. 360e(c)), as applicable.

scientific assessment and regulatory judgment to determine whether the drug's benefits outweigh the risks, and whether additional measures are needed and able to address or mitigate this uncertainty. Uncertainty in the benefit-risk assessment is discussed further in section III.B below.

- **FDA's regulatory options** to reduce uncertainties and manage risks. Examples of regulatory considerations include requirements for additional clinical studies conducted premarket or postmarket to further characterize safety, effectiveness, or dose response; additional product quality information; postmarket observational studies or enhanced pharmacovigilance; labeling content (e.g., limitations of use); or REMS.

B. FDA's Benefit-Risk Framework

FDA's vehicle for conducting and communicating its benefit-risk assessments is the Benefit-Risk Framework for new drug review.[17] The Benefit-Risk Framework (Figure 1) provides a structured, qualitative approach for identifying, assessing, and communicating the important considerations that factor into the benefit-risk assessment:

- The first two rows in Figure 1 outline the important dimensions of the assessment concerning the therapeutic context, including **Analysis of Condition** and **Current Treatment Options**, followed by the product-specific rows for the assessment of **Benefit** and **Risk and Risk Management**.

- The columns distinguish two important inputs to each dimension: The **Evidence and Uncertainties** that are most pertinent to the benefit-risk assessment and the **Conclusions and Reasons** based on the evidence and its strength, and the potential significance of the findings for each dimension. Evidence and uncertainties are relevant not only to the benefits and risks of the drug but also to the analysis of condition and current treatment options.

- Finally, the **Conclusions Regarding Benefit-Risk** overview integrates the evidence and uncertainties about the drug's benefits and risks and considers them in the context of the severity of the condition and the patients' current unmet needs.

[17] Information on development of the Benefit-Risk Framework is provided in FDA's 2013 PDUFA V Implementation Plan, "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making," available at https://www.fda.gov/media/84831/download and FDA's 2018 PDUFA VI Implementation Plan, "Benefit-Risk Assessment in Drug Regulatory Decision-Making," available at https://www.fda.gov/media/112570/download.

Figure 1. FDA's Benefit-Risk Framework for New Drug Review

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

FDA currently includes the Benefit-Risk Framework in its NDA and BLA review training, processes, and templates to support the conduct and communication of its benefit-risk assessment. CBER incorporates benefit-risk assessment through interdisciplinary review, and since 2013 has integrated the Benefit-Risk Framework into its clinical review template for its new BLA and supplement assessments. CDER has integrated the Benefit-Risk Framework into its clinical review and decisional memo templates since 2015. In 2019, as part of the New Drugs Regulatory Program Modernization,[18] CDER developed a new integrated review process and template[19] for its marketing application (NDA and BLA) assessments. This template includes interdisciplinary, issue-based sections that highlight important issues and address their impact on benefit and risk. The template also presents the Benefit-Risk Framework as a component of section 1., Executive Summary.[20]

[18] More information on the New Drugs Regulatory Program Modernization is available at: https://www.fda.gov/drugs/regulatory-science-research-and-education/modernizing-fdas-new-drugs-regulatory-program.

[19] This new process and template was announced in the *Federal Register* of June 27, 2019 (84 FR 30733), "New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication," available at https://www.federalregister.gov/documents/2019/06/27/2019-13751/new-drugs-regulatory-program-modernization-improving-approval-package-documentation-and.

[20] Information on how the Benefit-Risk Framework is incorporated into the review process is available in FDA's 2018 PDUFA VI Implementation Plan, "Benefit-Risk Assessment in Drug Regulatory Decision-Making," available at https://www.fda.gov/media/112570/download.

FDA's thinking on a drug's benefits and risks is often a topic discussed at product-specific advisory committee meetings.[21] FDA may use the Benefit-Risk Framework to communicate important considerations on the drug's benefit-risk assessment to the committee or to the public.

III. IMPORTANT CONSIDERATIONS FOR FDA'S PREMARKET BENEFIT-RISK ASSESSMENT OF DRUGS AND BIOLOGICS

A. Overview of Important Considerations

As evident from the multiple dimensions of the Benefit-Risk Framework, FDA's benefit-risk assessment integrates many different considerations. Table 1 provides examples of considerations that may be included in an assessment. The relevance and relative importance of any consideration depends on the specific details of the application.

Table 1: **Examples of Important Considerations for FDA's Premarket Benefit-Risk Assessment of NDAs, BLAs, and Efficacy Supplements**

Benefit-Risk Framework Dimension	Important Considerations
Analysis of Condition	• Context of use for proposed indication: intended medical use, target patient population, aspects of the condition (e.g., symptom burden) targeted by the treatment • Aspects of the indicated condition that are most relevant to, or have the greatest impact on, the intended population (e.g., incidence, duration, morbidity, mortality, health-related quality of life, important differences in outcome or severity in subpopulations) • Public health implications of the disease
Current Treatment Options	• Understanding of current approved treatments and standard of care, including their efficacy, safety, tolerability, and other limitations (e.g., subpopulations who do not respond to or do not tolerate treatment, curative versus palliative intent) • Efficacy and safety of other interventions used for the intended population, such as drugs used off-label or other nondrug interventions • Medical need for a new therapy in terms of efficacy, safety, tolerability, burden of existing treatments, etc.
Benefit	• Strengths/limitations of clinical trials, including design, and potential implications for assessing drug efficacy • Clinical relevance of the study endpoints: ability to measure or predict clinical outcomes of importance to patients • Description of the clinical benefits, including but not limited to: o Nature of the effect (e.g., survival, reduction of serious outcomes, reduction of symptoms, relevance of symptomatic benefit to patients) o Effect size and associated uncertainty (e.g., a confidence interval), including an interpretation of clinical importance o The distribution of treatment effects in the clinical trial population (e.g., presence of patients who experience a more substantial benefit such as long-term survival or marked improvement in symptoms, even if the mean response is modest)

[21] More information on FDA's advisory committees is available at: https://www.fda.gov/advisory-committees.

Benefit-Risk Framework Dimension	Important Considerations
	○ Time course and durability of effect ○ Benefit attributed to the drug when studied in combination with other therapies ○ Defined sub-populations achieving greater benefit • Benefit to a specific sub-population where there is an unmet need (e.g., patients who have not responded adequately to available therapies) • Generalizability of the demonstrated benefits to all populations likely to be prescribed the drug (e.g., older patients or patients with co-morbidities not extensively studied in the clinical trials) • Important characteristics of the drug (e.g., a less burdensome dosing regimen or route of administration)
Risk and Risk Management	• Strengths/limitations of the evidence regarding safety, and potential implications for assessing drug risks (e.g., due to limited database size and/or exposure duration, missing important sub-populations) • Observed adverse events or safety signals and their clinical importance, including: ○ Severity of the adverse event, the likelihood of its occurrence, reversibility, and the estimate of the effect size and its uncertainty (e.g., a confidence interval) ○ Ability to predict, monitor for, and/or prevent the adverse event ○ Impact of adverse events on drug adherence and the potential consequences • Level of certainty for a causal association between drug exposure and risk • Potential impact of product quality issue(s) that could negatively impact the drug's safety or effectiveness • Anticipated differences in safety that could occur in postmarketing compared with the clinical trial setting (e.g., because of less likelihood of appropriate monitoring, or use in patients that may be at higher risk of the safety event) • Potential for misuse or accidental exposure, and associated adverse consequences • Likely effectiveness of proposed approaches to managing risks (e.g., evidence from clinical trials that steps can be taken to reduce the risk)
Conclusions Regarding Benefit-Risk	• Overall conclusions about the quality and strength of evidence and the remaining uncertainties regarding benefits and risks • How therapeutic context affects the assessment of benefits, risks, and uncertainties • Relative importance of the benefits and risks in the overall indicated population, but also considering individual patient perspectives • The time course over which the benefits and risks occur (e.g., considering adverse events that may occur shortly after initiation for benefits that may take years to accrue) • Ability of patients and providers to clearly assess benefits from the drug (e.g., symptom relief, biomarker change), thereby informing treatment decisions (e.g., to discontinue drug if adequate response is not achieved) • Whether patients most likely to experience serious adverse events are also most likely to experience meaningful benefit (e.g., if adverse events reflect on-target pharmacology) • Whether the benefits and risks can be adequately communicated in product labeling to support informed individual benefit-risk assessments by patients and providers • Whether certain labeling (e.g., boxed warnings) and/or REMS is necessary to support favorable benefit-risk assessment • Whether a postmarketing study or clinical trial is necessary to assess a known serious risk or a signal of a serious risk

B. The Impact of Uncertainty on Benefit-Risk Assessment

FDA's benefit-risk assessment carefully considers the strength and quality of the evidence available and takes remaining uncertainties into account in every dimension of the Benefit-Risk Framework. Uncertainties that can affect benefit-risk assessments may include, but are not limited to:

- Limits on scientific understanding of the patient population and natural history of the condition, e.g., due to heterogeneity of disease manifestations and progression in the patient population, or lack of identification of risk factors or prognostic biomarkers.

- Aspects of the program or study design, such as the population, choice of controls, endpoints, duration, and data sources, as well as any differences between the clinical study and real-world use.

- Reliability of the estimates of benefit or risk based upon variability in estimated effects due to sampling (statistical uncertainty) or issues with trial conduct such as missing data, poor protocol compliance, etc.

- Limited understanding of the effects of the drug that may be used in combination with existing therapies (e.g., potential beneficial adjunctive effect, potential for adverse drug-drug interactions, etc.).

- Proposed risk management strategies, such as patient monitoring, which have not been studied in clinical trials, or that have been studied in clinical trials but would be potentially difficult to implement in practice.

- Limited patient input on disease burden and unmet medical needs, meaningfulness of potential benefits, and acceptability of risk tradeoffs and uncertainty.

- Introduction of a novel technology or control strategy in the drug's manufacturing process, or other potential issues regarding the product formulation or manufacturing.

Many sources of uncertainty can be anticipated and potentially avoided with careful attention to trial design during product development stages, as discussed further in section IV. At other times, uncertainties become apparent only after the trial evidence has been generated, such as the appearance of an unexpected safety signal. In such cases, identifying information to address these uncertainties becomes particularly important to support the benefit-risk assessment.

Therapeutic context plays an important role in FDA's assessment of the acceptability of uncertainty. For a drug intended to treat a serious disease with unmet needs, FDA may accept greater uncertainties about benefit or risk at the time of approval, for example through the

accelerated approval pathway.[22] In other situations, such as in the case of a drug that is intended to treat a non-serious disease and for which other therapeutic options exist, FDA would not be likely to accept as much uncertainty regarding either benefit or risk.

A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations. FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met. FDA therefore often exercises greater regulatory flexibility in these cases, in particular by accepting clinical trials that have lower sample sizes. This flexibility means that to be respectful of patients' willingness to participate in studies, it is important to maximize the potential for such clinical trials to provide interpretable scientific evidence about the drug's benefits and risks beginning from the earliest stages of drug development. Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features such as randomization, blinding, enrichment procedures, and adequate trial duration.[23]

C. The Role of Patient Experience Data in FDA's Benefit-Risk Assessment

FDA recognizes the importance of enabling meaningful patient input to inform drug development and regulatory decision-making, including in the context of FDA's benefit-risk assessment. Patients are experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcomes of medical treatment. Patient experience data can inform nearly every aspect of FDA's benefit-risk assessment throughout the drug lifecycle, including:

- Therapeutic context, such as:
  - Impact of the disease and its treatment on the patient
  - Patients' perspectives about available treatments and unmet medical needs
  - Enhanced understanding of the natural history of the disease or condition, including progression, severity, chronicity
- Potential benefits that are most meaningful
- Acceptability of risk and uncertainty
- Value and burden of risk mitigation efforts

[22] For more information about accelerated approval, see FDA's guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014), available at the FDA guidance web page.

[23] For further discussion of this issue, see FDA's draft guidance for industry *Rare Diseases: Common Issues in Drug Development* (January 2019) in particular, section VII., available at the FDA guidance web page. When final, this guidance will represent the FDA's current thinking on this topic.

If a methodologically-sound and fit-for-purpose[24] data collection tool(s) is used to collect patient experience data in a drug development program, the collected data can provide direct evidence regarding the benefits and risks of the drug and their importance to patients. During premarket review, FDA indicates in review documentation whether relevant patient experience data are submitted as part of the application, and whether relevant information was not submitted in the application but has informed FDA review nonetheless.[25]

As discussed in section II, FDA must balance the perspectives of patients with the judgments it must make regarding overall benefit-risk of a drug to the patient population. For example, even if some patients may derive benefit from a drug and express the desire for access to a drug, FDA would not approve the drug if it FDA concludes that the drug would lead to more harm in the indicated population overall–for example, if the drug is associated with significant risk, benefit is likely to be limited, and there is no way to identify those individuals who might benefit through the use of predictive biomarkers or other means. Nonetheless, FDA carefully weighs and considers the patient perspective. When patients indicate that a benefit is important to them in the treatment of their condition, this informs FDA's assessment of the extent of benefit.

IV. ACTIVITIES THAT OCCUR IN PREMARKET DEVELOPMENT THAT INFORM BENEFIT-RISK ASSESSMENT

Decisions and activities undertaken by sponsors in the development of their drugs, and the evidence generated to support their marketing applications, can have a significant impact on the agency's benefit-risk assessment. Examples of decisions and activities that may have bearing on a benefit-risk assessment include defining the target patient population, identifying unmet needs for these patients, selecting dose(s) for clinical trials, defining key features of trial design, selecting study endpoints, and incorporating risk mitigation practices into the clinical trial. It is important to note that these decisions and activities are also important in supporting any benefit-risk assessment the sponsor considers within their own drug development program.

A. Structured Benefit-Risk Planning During Drug Development

For the purposes of this guidance, structured benefit-risk planning is defined as a purposeful activity carried out by the sponsor to incorporate consideration of the product's benefit-risk assessment throughout the drug development lifecycle. Benefit-risk planning is most valuable in cases where a challenging benefit-risk assessment can be reasonably anticipated, either because the extent of benefit is expected to be modest or is highly uncertain, or when serious adverse

[24] Fit-for-purpose: a conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use. This definition is consistent with the definition of this term in the FDA guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020).

[25] Section 3001 of the 21st Century Cures Act (21 U.S.C. 360bbb-8c (b)(1)) states: "Following the approval of an application that was submitted under section 355(b) of this title or section 262(a) of title 42 at least 180 days after December 13, 2016, the Secretary shall make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application."

events of the drug can be anticipated (e.g., based on a suspected class effect, understanding of the mechanism of action, and/or early-phase or non-clinical safety findings). In cases where serious risks are anticipated, it is important to consider whether the risk can be balanced by a benefit of sufficient certainty and magnitude. The goal of benefit-risk planning would be to direct drug development towards reducing important uncertainties and establishing a favorable benefit-risk profile targeting a population that can be shown to benefit from the product (which may require limiting the population to those patients who are anticipated to obtain a greater benefit, or have a greater unmet need such as those failing available therapies), by minimizing the risks to patients, and by demonstrating that benefits outweigh the risks to the patient population.

Benefit-risk planning by the sponsor, beginning early in development, can add value by helping to ensure that the clinical trial data and other supporting information collected are best suited to support the benefit-risk assessment. Such planning can also support reassessments of the drug's benefit-risk profile, and inform potential changes in the development program, as new evidence is generated throughout development. In addition to supporting premarketing development and evaluation, planning for postmarket benefit-risk assessment during the premarket stage can inform approaches to collecting additional information in the postmarket setting to further reduce uncertainties.

Benefit-risk planning includes identifying, as early as possible, the most important potential benefits and risks of the drug, so that they can be carefully evaluated. This planning also includes careful consideration of how to focus the development program to best inform the eventual benefit-risk assessment. Examples that illustrate this concept include:

- Identification of patients (e.g., utilizing a predictive biomarker) who are more likely to experience greater expected benefit or less likely to experience serious adverse events of the drug, thereby enabling determination of a population for whom the drug may have a more favorable benefit-risk profile.

- Collection of sufficient data throughout development to inform dose exposure response for both efficacy and safety/tolerability and integrating this information to identify doses that can optimize benefit relative to risk and inform dosing recommendations.

- Selection of a primary efficacy endpoint that is a direct measure of how a patient feels, functions, or survives–or is a surrogate endpoint for which the relationship between an effect on the surrogate endpoint and the clinical outcome of interest is well understood–in order to obtain a reliable estimate of and reduce uncertainty about direct patient benefit, especially when serious risks may be associated with the drug.

- Use of an active control arm in circumstances when it may be critical to ensure that the drug does not have an unacceptable benefit-risk profile compared to an approved, alternative therapy, or to show that the drug is more effective than available therapy.

- Enriching a trial to enable the demonstration of benefit in a specific subpopulation (e.g., patients who do not respond to or who do not tolerate a standard of care treatment).

- In planning the sample size and duration of a clinical trial, consideration of not only the efficacy assessment, but also the degree of precision that will be provided for evaluating an anticipated serious risk.

- Prospective collection of data to evaluate a potential serious risk, such as by actively ascertaining the occurrence and nature of the adverse event of interest using targeted case report form prompts and/or independent adjudication.

- Implementation of appropriate risk mitigation measures into the clinical trial with the ability to prevent or monitor for anticipated serious adverse events, in order to provide sufficient evidence that the risks can be adequately managed post-approval.

The optimal timing, scope, and level of effort of benefit-risk planning may vary depending on the sponsor's expectation of the degree of complexity regarding the eventual benefit-risk assessment of the marketing application. Benefit-risk planning can take many forms. The ICH guidance for industry M4E(R2), section 2.5.6, and the July 2016 ICH guidance for industry ICH *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* (ICH E2C(R2)), section 3.18, may provide a useful starting point for sponsors to think through benefit-risk planning throughout the lifecycle.[26] In addition, various qualitative structured approaches and supporting tools tailored for drug development and evaluation (e.g., value trees, effects tables, forest plots) have been developed and may be useful to support sponsors' benefit-risk planning, assessments, and communications with FDA.[27]

B. Appropriate Interactions Between a Sponsor and FDA During Drug Development To Inform Benefit-Risk Planning

FDA can provide insight and regulatory perspective that can inform a sponsor's benefit-risk planning appropriate to the issues identified at a particular stage of development. The End of Phase 2 (EOP2) meeting is typically a critical timepoint where discussions with FDA on benefit and risk considerations may be especially important and can influence the design of phase 3 studies in ways that can enhance the characterization of the drug's benefits and risks, including decisions on study design, selection of appropriate patient populations, enrichment strategies, clinically meaningful endpoints, trial duration, dose-response assessment, and trial sizes. Thoughtful planning can also enhance the assessment of risk needed to support informed benefit-risk assessment. These discussions at EOP2 can be particularly important when preclinical, early clinical, or other data identify a potential safety issue that would require greater certainty about the drug's benefits and/or risks to support approval.

Although it is important to discuss benefit-risk planning at EOP2, in some situations there may be earlier points in a product's development when communication between the Agency and the

[26] Available at the FDA guidance web page.

[27] Hughes, D, E Waddingham, S Mt-Isa, A Goginsky, E Chan, GF Downey, CE Hallgreen, KS Hockley, J Juhaeri, A Lieftucht, MA Metcalf, RA Noel, LD Phillips, D Ashby, and A Micaleff, 2016, Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations, Pharmacoepidemiol Drug Saf, 25(3):251-262.

sponsor regarding benefit and risk considerations would be useful. These communications could involve deliberations regarding the clinical meaningfulness of a purported benefit or concern for non-clinical safety signals at the pre-IND phase for first-in-human studies. They could also involve considerations on the best design to characterize benefits and risks where the population is limited or vulnerable, such as for rare or serious diseases or pediatric populations.

Typically, discussion of benefit-risk considerations and benefit-risk planning occurs within the standard processes for formal meetings between FDA and sponsors.[28] Sponsors can add "benefit-risk considerations" as a proposed question and/or agenda item and provide relevant supplementary information in the meeting package. The type of input that FDA can provide on benefit and risk considerations depends on the product, indication, current therapeutic context, stage of product development, and uncertainties associated with the benefit, risk, or other development issues. FDA's input on these topics may evolve as more information becomes available throughout development. FDA's final premarket benefit-risk assessment is based on complete information submitted as part of an NDA or BLA.

C. Collecting Patient Experience Data During Development To Inform Benefit-Risk Assessment

Patient experience data can help inform critical aspects of a drug development program, and benefit-risk assessment more broadly. For example, patient experience data collected early in the development program can help identify unmet patient needs and define the target patient population. Patient experience data can also inform the assessment of the clinical relevance of the study endpoints, that is, to help identify endpoints that measure or predict clinical outcomes of importance to patients. FDA encourages sponsors who are considering collecting and utilizing patient experience data as part of their evaluation of effectiveness or safety to have early interactions with FDA during the design phase of such studies and obtain feedback from the relevant FDA review division on appropriate research design and any applicable regulatory requirements.

As part of the Patient-Focused Drug Development[29] and Science of Patient Input[30] 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 and is developing a series of methodological guidances[31] on these approaches. A primary component of this guidance

[28] See FDA's draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017), available at the FDA guidance web page. When final, this guidance will represent the FDA's current thinking on this topic.

[29] More information on patient-focused drug development is available at https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

[30] More information on the science of patient input is available at https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/center-biologics-evaluation-and-research-patient-engagement-program.

[31] More information on FDA's patient-focused drug development guidance series "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product

series is to provide a patient-focused outcome measurement approach to clinical outcome assessment (COA)32 selection and/or development for clinical trials. Collecting robust patient input on the symptoms or other aspects of their condition that matter most to patients can inform and strengthen the rationale for the endpoint selection and development of COAs.

Patient preference information (PPI)[33] is another type of patient experience data. PPI may be useful to sponsors at various stages of drug development, including informing the therapeutic context, identifying endpoints, and informing benefit-risk assessment. It can be collected for a specific drug development program, or more broadly within a therapeutic area. PPI may be best suited to inform regulatory decision-making when: 1) significant risks of treatment or uncertainty about risks exist relative to the expected benefits; 2) patients' views about the most important benefits and risks vary considerably within a population; and/or 3) when patients' views as to the most important benefits are expected to differ from those of healthcare professionals. If available, PPI would be considered within the context of FDA's assessment of the drug's efficacy and safety to the patient population, although it would not, for example, overcome significant safety issues or lack of therapeutic benefit.

Use of a carefully planned, fit-for-purpose design can increase the ultimate usefulness of the PPI. Before using any approach, sponsors should consider its utility, complexity, the extent to which the approach can address the research question, and the interpretability of the results. When included in a regulatory submission, PPI should be collected through a formal study with pre-specified protocols and analysis plans and should include a broad and representative sample of patients. Additional information about patient preference studies may be found in section IV. of FDA's guidance for industry *Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling* (August 2016).[34]

Development and Regulatory Decision Making" (August 2019), available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[32] Clinical outcome assessment (COA): Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment. There are four types of COAs: patient-reported outcome (PRO), clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO), and performance outcome (PerfO). This definition is consistent with the definition of this term in the FDA guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018).

[33] Patient preference information (PPI): Assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. The methods for generating PPI may be qualitative, quantitative, or mixed methods. For further discussion, see FDA's guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018).

[34] See section IV., Recommended Qualities of Patient Preference Studies. This guidance for industry was released by FDA's Center for Devices and Radiological Health (CDRH) and CBER.

D. Conducting Additional Analyses To Inform Benefit-Risk Assessment

Benefit-risk assessment inevitably involves a qualitative, subjective judgment that weighs data and information about the drug's benefits and risks and considers uncertainties within a specific therapeutic and regulatory context. Nevertheless, additional benefit-risk analyses to help inform the overall benefit-risk assessment may add value in some circumstances, such as decisions involving complex tradeoffs between the drug's expected benefit and risks, or significant or novel uncertainties regarding the drug's benefits and risks. Although additional benefit-risk analyses may add value in these situations and others, it may not be appropriate in all circumstances, and it cannot overcome significant issues in a development program, such as inadequate assessment of risk mitigation in the clinical trial.

Additional analyses can take various forms, for example:

- Estimation of important clinical benefit or risk outcomes that were not directly measured or sufficiently assessed in the clinical trial (e.g., extrapolation from a primary surrogate endpoint).

- In certain situations (e.g., diagnostics), modeling of benefit and risk outcomes or public health outcomes that could be expected in the real-world setting, accounting for aspects regarding the patient population or setting of use that may extend upon the clinical trial setting (e.g., the public health impacts of false negative diagnoses).

- Integrating benefits and risks in a combined analysis and/or incorporating information about desirability of outcomes and tradeoffs between benefits and risks.

Some situations where additional analyses may add value can be anticipated early in development, notably in the case of a drug expected to have a serious risk. When anticipated, consultation with FDA and careful planning early in drug development can increase the potential value of the benefit-risk analysis by ensuring that appropriate information is collected through studies, trials, or other approaches. Pre-specification of data collection and benefit-risk analysis can also ensure transparency and facilitate interpretation of results. In cases where challenging benefit-risk issues are not anticipated, such as a safety signal arising in pivotal trials or postmarket, additional benefit-risk analyses can still be useful. However, the utility may be limited if the critical data are not available or cannot be appropriately collected during the available time frame.

There are many approaches to conducting additional benefit-risk analyses, and numerous reviews of methodology are available.[35] This guidance does not prescribe specific approaches for sponsors to follow in drug development. The appropriate method(s) will depend on the benefit-risk issue and the information available. The interpretability and usefulness of results rests on the validity and assumptions of the selected method and the underlying data, both of which

[35] Mt-Isa, S, M Ouwens, V Robert, M Gebel, A Schacht, and I Hirsch, 2015, Structured Benefit-Risk Assessment: A Review of Key Publications and Initiatives on Frameworks and Methodologies, Pharm Stat, 15(4):324–332.

should be fully reviewable by the Agency. Generating rigorous evidence to inform FDA's benefit-risk assessment calls for careful planning and should involve prospective interaction with FDA, as well as complete documentation of selection of methodology, data, assumptions, results, and sensitivity analysis of uncertainties. The analysis output is typically not useful in isolation for regulatory or other types of decision-making, and the Agency will consider additional benefit-risk analysis as one part of the overall qualitative benefit-risk assessment and regulatory decision-making process.

E. Presenting Benefit-Risk Considerations in the Marketing Application

The effective communication by sponsors of the drug's benefits, risks, and uncertainties is important to informing the benefit-risk assessment that supports regulatory decision-making, particularly when serious risks are involved. A critical source of benefit-risk information is the sponsor's NDA or BLA. As part of an NDA submission, the sponsor must provide "[a]n integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in labeling" (see 21 CFR 314.50(c)(5)(viii)). The ICH M4E(R2) guidance, revised in 2016 and adopted by FDA as a guidance for industry in July 2017, provides recommendations on the presentation of benefit-risk assessment information in premarket applications.[36] In addition, in light of the considerations described in section III. above, the following information may facilitate FDA's benefit-risk assessment:

- Description of the clinical importance of key benefits and risks, including:
  - Discussion of the magnitudes of effects and treatment effects (difference between drug and comparator). For binary outcomes, this includes treatment effects on both the absolute difference and relative scales. For continuous outcomes, this includes context on the assessment scale, mean baseline values, understanding of meaningful within-patient change, and distribution of effects sizes in the population.
  - Exploration of the nature of effects (e.g., consideration of time course and durability of the drug's effect, the clinical importance of benefit of a particular magnitude, and patient input on importance).
- Estimates of the statistical uncertainty around the magnitudes of the most important benefits and potential risks (e.g., with confidence intervals).
- Presentation of a graphical or tabular summary of results for the most important benefits side by side or juxtaposed with important potential risks. Care should be taken to ensure that such presentations provide a complete and balanced picture of benefits and risks that is easily interpretable. This includes, for example, ensuring that all important benefit and risk outcomes are included and clearly indicating when multiple endpoints used to assess the same benefit or risk outcome are presented.

[36] See the discussion of CTD section 2.5.6. in FDA's guidance for industry *M4E(R2): The CTD—Efficacy* (July 2017).

- Discussion of additional sources of uncertainty about benefits and/or risks, untested risk management strategies, or potential differences between aspects of the clinical trial and expected real-world use (e.g., population, adherence, safety monitoring).

These same considerations may be useful for sponsors when considering how to present this type of information at product-specific advisory committee meetings.

V. BENEFIT-RISK ASSESSMENT CONDUCTED IN THE POSTMARKET SETTING

Benefit-risk assessment does not end with FDA's approval of a drug. FDA considers a lifecycle approach to a drug's benefit-risk assessment, acknowledging that our understanding of both the product's benefits and risks often changes over time as new information about the product's effectiveness or safety becomes available. When FDA considers a drug's benefits and risks and uncertainties in the postmarket setting, it does so in light of new information about a drug's risks and benefits that is available post-approval. Postmarket evidence to inform benefit-risk assessments can come from a diverse set of sources, such as the medical literature, postmarketing studies, adverse event reports, medication error reports, product quality reports, and in some cases, from new data obtained from drugs of the same class. This information can be collected for specific purposes–such as for a postmarketing study requirement or for REMS assessments–or it can be generated through routine surveillance and pharmacovigilance. In some cases, uncertainty about serious safety concerns identified in the premarket review may decrease over time as the body of evidence builds (including from postmarketing clinical trials, studies, and surveillance). In other cases, a new safety signal may emerge in the postmarketing setting, especially for rare adverse events that were not observed in pre-approval clinical trials.

FDA may conduct a structured benefit-risk assessment, guided by the Benefit-Risk Framework, when new information emerges that warrants a reexamination of the benefit-risk profile of the marketed drug under the current requirements for approval. Examples of regulatory decisions that may be informed by such assessments include addition, modification, or removal of a REMS, initiation or release of postmarketing study requirements, labeling changes (e.g., addition, revision, or removal of a boxed warning), and, rarely, marketing withdrawal.[37] FDA's benefit-risk assessment in the postmarket setting generally considers the strength of the evidence evolving in the postmarket setting, remaining uncertainties about the drug's benefits and risks, how the drug is used in the postmarket setting, the evolving therapeutic context, and the availability of alternative treatments.

Adopting a lifecycle approach to benefit-risk planning can help inform sponsors' postmarketing activities and decisions. Sponsors may find a structured approach, guided by the Benefit-Risk Framework or the July 2016 guidance for industry ICH E2C(R2), useful to support their generation and evaluation of new information and decisions made regarding the new information.

[37] As noted above, these regulatory decisions are made in accordance with specific, applicable legal and regulatory authorities and criteria, most of which are not discussed in this guidance.

Periodic reporting is an important mechanism for sponsors to communicate information to FDA that can inform lifecycle assessment of a marketed drug's benefit-risk profile.[38] The ICH guidance for industry E2C(R2) provides recommendations on developing an optional Periodic Benefit-Risk Evaluation Report (PBRER) with the objective to:

> [P]resent 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.[39]

FDA's November 2016 guidance for industry *Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)* recommends the procedures that sponsors should follow if they wish to submit a PBRER.[40] If sponsors wish to submit a PBRER, FDA recommends that sponsors follow the format described in the most current version of the ICH E2C guidance for industry.

Sponsors, however, should not wait for a periodic safety update to report a potentially serious safety concern. New information about a potential serious safety concern that could have an impact on a drug's benefit-risk profile should be communicated promptly to FDA.[41]

[38] Sponsors are required to submit certain adverse event reports to FDA (see 21 CFR 314.80 and 600.80).

[39] See ICH E2C(R2), page 2.

[40] To submit the PBRER in lieu of submitting the periodic adverse drug experience report or periodic adverse experience report as required under 21 CFR 314.80(c)(2) or 600.80(c)(2), applicants must request a waiver under 314.90(a) or 600.90(a), respectively.

[41] Sponsors are required to submit certain adverse event report information within 15 days (see 21 CFR 314.80(c)(1) and 600.80(c)(1)).