November 29, 2021

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2020–D–2316: Benefit-Risk Assessment for New Drug and Biological Products; Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance *Benefit-Risk Assessment for New Drug and Biological Products* (Draft Guidance or Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO believes the Draft Guidance provides helpful information to sponsors regarding the benefit-risk assessment process and appreciates the Agency's current approach to using a structured approach to benefit-risk assessment that is sufficiently flexible to allow for the appropriate evaluation of product- or disease-specific contextual considerations. To further enhance the Guidance, we believe that a number of areas would benefit from more case studies, examples, and references. We have identified through our comments areas where these additions would be beneficial.

In the letter that follows we offer comments regarding additional emphasis on Patient Experience Data (PED), communicating benefit-risk, sponsor-FDA interactions and discussions, consistent and transparent implementation, methodologies, therapeutic context, and other considerations. We also provide detailed, specific line edits and recommendations in the chart that follows.

I. Additional Discussion and Emphasis on Patient Experience Data and its Utilization in the Benefit-Risk Assessment

We appreciate the inclusion of FDA's views on the relevance of Patient Experience Data (PED) including Patient Preference Information (PPI), to FDA's benefit-risk assessment. We believe that it would be valuable to provide additional detail on how PED will be considered in in the overall benefit-risk assessment (e.g., the role PED played in informing the FDA decision on overall benefit-risk). The Guidance should also integrate references and discussion of how PED can inform various aspects of benefit-risk throughout the document. Currently, PED is only acknowledged in a separate section towards the end of the document and in a section on

uncertainties. We also encourage FDA to update the benefit-risk table section of the Guidance to include the ways in which PED could be included for each dimension in the table.

Within the Voice of the Patient (VoP) Report, FDA sometimes includes analysis of a condition from the patient perspective. This information should be utilized more by FDA to inform discussion on benefit-risk and unmet medical need and should be discussed in this Guidance. It would be helpful to understand if FDA has a policy and expectation of review teams to use existing benefit-risk context from FDA's own VoP reports. We recommend that FDA discuss how FDA-generated PED (e.g., VoP Report) may be evaluated and used differently than externally-generated PED in a benefit-risk assessment and the rationale for any differences.

We commend FDA for recognizing the importance of enabling meaningful patient input to inform regulatory decision-making in the context of FDA's benefit-risk assessment; however, it is also important that FDA's benefit risk assessments using PED are conducted consistently within and across Divisions and that the process is robust and transparent to Sponsors and patients. To meet these important objectives, we support: 1) the development of internal FDA policies and procedures (e.g., a new MAPP and/or SOPP) that promotes the rigorous, consistent, predictable and timely review of patient preference and patient experience data (see comment for lines 191-197 in the following chart), 2) the development and implementation of FDA internal training programs, and 3) the acquisition of additional review expertise to meet the increasing amount of patient experience data and patient preference information that will be submitted in applications. We recognize that many of these recommendations are included in the Eastern Research Group Report *Assessment of the Use of Patient Experience Data in Regulatory Decision-Making.*[1]

Finally, we encourage FDA to include in Section IV D of the Guidance additional clarity and discussion regarding the circumstances when additional quantitative or weighted benefit-risk analysis would likely be of greater value to the assessment.

II. Timing of Sponsor-FDA Engagement and Discussions

We appreciate that the Draft Guidance recommends key timepoints to seek FDA input on the benefit-risk assessment, however, we note that it would be useful to also provide guidance on how to address some of the recommendations, such as the design of a pivotal study to reduce uncertainties.

It would be helpful for this Guidance to expand the discussion regarding how early interactions may be used for benefit-risk planning. While FDA and Sponsors recognize the value of these interactions, they can be challenging to efficiently schedule, with the right people at the right time. (Please see additional comments to lines 406-437 in the following chart.)

The Guidance should illustrate how FDA's benefit-risk framework could be used to shape sponsor-FDA interactions/discussions at milestone periods during drug development (Phase 1, Phase 2, Phase 3, etc.) to enhance communication and alignment on patient-focused drug

[1] Eastern Research Group Assessment of the Use of Patient Experience Data in Regulatory Decision-Making 2021

development. BIO would like to refer FDA to the BIO white paper[2] on the life cycle approach to benefit-risk assessment regarding Sponsor-FDA interactions and discussions at key milestones included.

A key concern for sponsors is how FDA determines that limiting the indication statement is justified based on the Agency's benefit-risk assessment. Sometimes the indication statement reflects a sub-population of those studied in clinical trials; however, it is often unclear how FDA arrives at the decision to limit the indication.

III. Communication of the Benefit-Risk Assessment

The PDUFA VI commitment letter[3] highlighted three core areas this Guidance would cover, the third being:

> "*iii. Discuss appropriate approaches to communicate to the public FDA's thinking on a product's benefit-risk assessment, such as through product specific discussions using the benefit-risk framework at AC meetings.*"

However, the introduction that lays out the purpose and scope of the Guidance is silent on the communication topic, and the rest of the Guidance is also light on communication aspects. BIO believes that improved communication would help inform individual benefit-risk assessments and treatment decisions. As such, we suggest adding a dedicated section that includes FDA's current thinking on appropriate approaches to communicate a product's benefit-risk assessment.

Further, the Draft Guidance is silent on the topic of applying risk communication and health literacy best practices when communicating FDA's thinking regarding a benefit-risk assessment to patients or the public or when seeking public or patient input on materials related to the benefit-risk assessment of a drug or biologic product under review (e.g., in Advisory Committee briefing materials).

We suggest including a statement and description of how the Agency would apply risk communication and health literacy best practices when communicating FDA's thinking regarding a benefit-risk assessment to patients or the public or when seeking public or patient input on materials related to the benefit-risk assessment of a drug or biologic product under review (e.g., in advisory committee briefing materials). The Agency could cite its existing guidance on risk communication and health literacy.[4,5,6]

It should be clarified in which situations it is relevant to add patient perspective and / or preferences to the label; for example, when FDA has taken the information into account for decision making or when the information may be relevant to inform physician-patient discussions about the most appropriate treatment.

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[2] A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework, BIO
[3] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022
[4] Risk Communication, FDA
[5] FDA Strategic Plan for Risk Communication and Health Literacy 2017 - 2019
[6] Communicating Risks and Benefits: An Evidence-Based User's Guide | FDA

Further, CDRH has published a website of use of preference information in regulatory decision making[7] and CDRH's preference sensitive priority areas[8]. We encourage CDER and CBER to develop a similar resource for sponsors.

IV. Post-Marketing Considerations

As currently written, the Guidance does not fully integrate post market benefit-risk assessment throughout all relevant conceptual areas. BIO recommends FDA provide additional guidance on how the overall benefit-risk framework may be affected and conducting structured benefit-risk assessment by a marketing authorization holder in the post-market setting. This will provide broader, holistic lifecycle level of guidance.

For example, Figure 1 outlines FDA's benefit-risk framework of a structured and qualitative approach for new drug review, but each dimension lacks full insight of approaching the considerations in the post market setting. FDA should clarify how post market data such as PMR outcomes, RWE, REMS assessments, PED and other types of data. would be considered in any re-examination of the benefit-risk profile of the drug after approval, including any additional analyses which may provide value. FDA could also consider development of an analogous post-market focused figure within the guidance.

Additionally, FDA should expand on the role of patient experience data such as patient preference information, and patient reported outcomes in the post market setting.

FDA should also provide insight of how burden and access in the context of risk mitigation activities (i.e., REMS) may impact benefit-risk assessment in the post-market setting. For example, when proposed risk mitigation strategies are well-integrated in practice, how FDA will consider the value of the decreased burden of modification of risk mitigation efforts in the assessment of benefit-risk.

V. Therapeutic Context

We acknowledge FDA's considerations regarding risk tolerance within the context of available therapies [lines 133-135]; however, the Guidance should address the potential benefits of having a variety of therapeutic options that may be effective to address the unique treatment needs of patients. Further discussion of the specific health considerations and preferences of individual patients may be helpful in describing a more nuanced version of benefit-risk. It will often be the case that multiple products approved for the same indication have strengths and weaknesses in providing a viable therapy to patients. For example:

- A particular therapy may be more attractive to some patients' needs (oral therapy vs. injection; self-administration vs. physician administration; allergies to excipients) that may also consequently promote treatment adherence and therefore potential benefits.

[7] https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/patient-preference-information-ppi-medical-device-decision-making
[8] https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/patient-preference-sensitive-areas-using-patient-preference-information-medical-device-evaluation

- There may be situations where patient preferences and needs may play a critical role in differentiating between products for the same disease. Patients may differ not only in their physical responses to therapies, but in their functional needs and the ways those therapies meet their needs. For example, pain is a highly subjective but important endpoint. One patient may want or need a complete response to a medication that takes away their pain, even if it leaves them unable to drive on their own. Another patient may desire decreased pain but the ability to be more active. Measuring physical responses or markers of decreased pain alone will not meet both patients' needs. They may need different medications in order to function in their everyday lives or
- A therapy may be more effective or preferred for select subpopulations, to the extent that the benefit-risk calculus may differ for those subpopulations.
- Benefit-risk evaluation for new and innovative treatment options is an area where PPI and PED can provide potentially important information for regulatory decision making.

We believe that labeling can often appropriately address the roles of multiple products in treating a disease, for example describing the populations and limitations. In summary, a discussion of both how having multiple therapeutic options can be beneficial, and how labeling may be used to manage treatments in subpopulations, would be helpful.

While we appreciate the discussion of therapeutic context and multiple treatment options and believe it provides appropriate context for FDA benefit-risk assessments, we recommend FDA clarify the role of this information and how its considerations of this information still fit within statutory approval standards. Specific examples of FDA prior regulatory actions could help illustrate how FDA considers this information.

Additionally, the Draft Guidance acknowledges that, in some circumstances, it may be important to collect data on specific subpopulations, as identified during development. In those contexts, the Guidance recommends, for example, the use of targeted case report forms to further characterize benefits, risks, and other important factors as relevant to that subpopulation. It would be helpful for FDA to include in the Final Guidance its recommendations for capturing or characterizing the impact, if any, on overall study data in cases where study plans are adjusted to gain additional data on a specific study population.

VI. Considerations for Future Guidance

While outside the scope of this Guidance, BIO believes there are a number of related topics that should be considered for future guidances. These include:

- Additional detail on how patient experience data will be considered in the structured benefit risk framework
- Guidance on how sponsors can communicate to healthcare providers, patients, and other shared decision makers on benefit-risk, in particular with regard to PED such as patient preference information (PPI), and patient reported outcomes (PRO) and other types of clinical outcome assessments.

- Further detail regarding the collection of PPI and other PED would be helpful. In particular, we recommend including additional information about the method of collection and research designs as well as specific examples of types of data.

VII. Conclusion

BIO appreciates this opportunity to submit comments regarding the Draft Guidance *Benefit-Risk Assessment for New Drug and Biological Products.* Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed and we look forward to future opportunities to collaborate with the Agency on this important topic.

Sincerely,

/s/
Katherine Donigan, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 68-73:	The Draft Guidance explains that FDA evaluates effectiveness according to the SEE standard and that safety is evaluated by determining if benefits outweigh risks.	BIO suggests that this section of the Guidance further elaborate that the regulatory decision to approve a product is a two-step process grounded in FDA's determination that a drug is effective and safe. FDA must first determine whether the drug is effective as defined in FDA's statute. If the Agency concludes the drug is effective, FDA can then assess whether the drug is safe. While no written standard exists for determining that a drug is safe, it has long been interpreted as FDA's conclusion that a drug's by concluding that the benefits outweigh its risks. Such a description of the Agency's decision process offers a clear view of how effectiveness and safety are incorporated into FDA's regulatory decisions. This level of clarity would be helpful if it were to include in this Guidance.
Lines 73-74:	The Draft Guidance states, "Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks." Demonstration of safety typically requires analysis of safety data during drug development and consideration as to whether and how the product safety profile is manageable, which factors into benefit-risk assessment.	BIO suggests editing the text to read: "Because all drugs can have adverse effects, the demonstration of manageable safety risks under the condition of use is required to support a favorable benefit-risk assessment ~~requires a showing that the benefits of the drug outweigh its risks~~."
Lines 80-84:	The Draft Guidance discusses the applicability of benefit-risk assessments to an NDA or BLA. However, BIO notes that typically, benefit-risk assessment is provided by sponsor in the clinical	BIO suggests editing the text to include "NDA, or BLA, and supplements for new and/or extended indications".

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	overview for not only new marketing applications, but also for new and expanded indications, especially in new target populations for additional uses.	
Lines 86-90:	The Draft Guidance discusses benefit-risk assessment being straightforward or more challenging.	It would help if the definition of "serious risk" was more specific than the definition provided in lines 89-90. Later in the document, there is also reference to "Important" risks (lines 562-567) – are these meant to be the same as "serious" risks mentioned earlier in the document? Also, do the "important" potential risks in this document carry the same relevance/definition as in the EU regulatory environment? We suggest including a single reference to serious risk if possible and providing a clear definition of it.
Lines 90-92:	For both drugs, those with "straightforward" and with the "challenging" risks the agency requires risks to be "sufficiently characterized". The Guidance does not reflect on necessity and feasibility of determining the benefit-risk profile for drugs with risks that are not "sufficiently characterized" (e.g., for drugs with breakthrough or fast track designation)/	We suggest clarifying necessity and feasibility of benefit-risk assessment for the products filed based on limited data.
Lines 93-96:	The Draft Guidance states, "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 addition to the points listed, determination of the benefit and risk may also depend on the patients' tolerance of risk and desirability of benefit which may vary given their disease and treatment experience. We suggest the text include "context of use" as it plays a major role in sponsor and regulator assessments in the target population.

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		Also, BIO suggests substituting "current treatment options" for "current treatment landscape" for specificity. Notably, throughout the Guidance there are references to different terms for what seem to be the same concepts, e.g., "treatment landscape," "treatment options," as well as "treatment context". We suggest utilizing the same term throughout. Further, we believe that the determination should also include the general or specific preferences of the patient population that the drug is targeted for (not only mentioning patient population). Adding patient preferences/ patient insights aspect consistently in this guidance will help sponsors consider including patient insights more comprehensively as part of the totality of evidence. We therefore recommend the following changes: "This determination requires a thorough assessment of the available evidence in the context of use, 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~~ options."
II. FDA'S APPROACH TO THE BENEFIT-RISK ASSESSMENT OF NEW DRUGS AND BIOLOGICS		
A. Regulatory Background		
Lines 98-99:	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.	It would be helpful for the Guidance to provide specific examples for gene therapy development. Additional commentary would be helpful on how theoretical risks that have not been observed during pivotal studies influence B/R assessments. Importantly, it would be helpful for FDA to clarify and ensure that theoretical risks don't adversely impact the benefit risk balance for the product; and that sponsors should instead account for that risk in the post market considerations.

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Line 107:	Throughout the Draft Guidance, the benefit-risk assessment in subgroups has been suggested. Knowing the subgroup findings are prone to biases and results can be misleading, the believability of subgroup findings, particularly those without stratification and randomization guarantee, is a major issue.	The document should highlight the issue with post-hoc subgroup findings with words of caution; and further elucidate the importance of selecting and applying robust methodologies for subgroup identification. It should advise careful analyses while dealing with subgroups to identify potential biases and confounding and to minimize any negative impacts in analyses. However, the benefit with deliberate identification of higher risk patient subgroups (e.g., patients who are able to become pregnant, renally impaired, certain genotypes, etc.) is imperative in understanding uptake of risk minimization approaches and their effectiveness for those subgroups.
Lines 127-130:	The FDA intends to incorporate broader public health consideration when assessing benefit-risk for the controlled substances	Assessment of benefit-risk should be limited to populations that may experience both risks and benefits of the drug product, e.g., population intended for treatment. Patients benefiting from treatment should not be denied access to controlled substances because of risk for "others" who intentionally misuse it.
Line 137:	The Draft Guidance discusses the therapeutic context of a drug and mentions "and how well patients' needs are being met by currently available treatments." We note that product drug development typically addresses unmet **medical** needs, hence emphasis is being made for clarity.	We suggest editing the text for clarity as follows: "and how well patients' medical needs are being met by currently available treatments."
Lines 138-145:	FDA's current text reads as follows: "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	We recommend that FDA further describe what the agency means by 'lower tolerance' in this section. For example, assuming a drug has demonstrated efficacy, does this mean the agency would always reach a conclusion that the benefit-risk assessment is unfavorable given the relative assessment

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	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."	of safety profiles? Or would the agency seek to address the risk through risk management actions or a second-line indication?
Lines 147-150:	We agree that it is a positive step forward and appropriate to include patient experience data within the list of evidence that informs the FDA decision on a marketing application. The Guidance states, "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." While the list includes epidemiological data, and while some patient experience data may be Real world data The broader complete category of RWD and real-world evidence (RWE) is another important category of evidence that can have an important role in informing FDA benefit-risk decisions; therefore, please consider expressly including.	BIO asks the Agency to consider expressly adding "real world data (RWD) and real-world evidence (RWE)" as an additional source of evidence that can inform FDA's understanding of the benefits and risk of a drug or biologic.
Lines 147-150:	BIO notes that pre-marketing data based on clinical studies may have better quality in terms of less chance	BIO suggests adding wording to clarify how the different types of data fit into the analysis.

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	of being biased as compared to the post-marketing data. Will pre-marketing data and post-marketing data be treated differently?	
Lines 152-160:	The Guidance mentions "uncertainty". In the evaluation, potential bias might be a more fundamental issue.	BIO suggests adding text regarding potential biases in the data/evidence being used in the benefit-risk assessment.
B. FDA's Benefit-Risk Framework		
Lines 175-178:	The Draft Guidance describes the benefit-risk framework and states "followed by the product-specific rows for the assessment of Benefit and Risk and Risk Management." The intended condition of use proposed or approved in the product label is predicated on substantial evidence that supports a favorable benefit-risk assessment. Endpoints or surrogates from clinical trials are specific to assess unmet medical needs (i.e., key benefits), and significant risks (i.e. key risks) which are important to the patient's wellbeing. It's important to focus benefit-risk assessment on key benefits and key risks that support the condition of use in the targeted population.	We suggest editing the text to read: "followed by the product-specific rows for the assessment of Key Benefit and Key Risk and Risk Management."
Line 181:	The Draft Guidance states, "Uncertainties that are most pertinent to the benefit-risk assessment…"	BIO suggests differentiating uncertainty due to chance and due to bias and discussing them accordingly.
Lines 191-197:	The Draft Guidance includes FDA's Benefit-Risk Framework for New Drug Review.	Given that FDA includes the Benefit-Risk Framework in its NDA and BLA review training, processes, and templates, we suggest that the framework include a prompt for reviewers to specifically note how any PED was used to inform any aspect of the structured benefit-risk assessment. This could help improve transparency and promote more consistent evaluation of PED, which, in turn, would help promote more consistent collection and submission of PED on the part of Sponsors.

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Lines 195-204:	The Draft Guidance describes the implementation of the Benefit-Risk Framework in its benefit-risk assessment along with templates and CDER's new integrated review process and templates for marketing application assessments.	As the implementation of the Benefit-Risk Framework started before the 21st Century Cures Act's requirements to make public how PED is considered in reviews (§3001), it would be helpful to understand how PED considerations can be made more visible within the B-R Framework in order to align/connect the review requirements and increase transparency on how PED has influenced regulatory decision-making.
Lines 207-209:	The Draft Guidance states, "FDA's thinking on a drug's benefits and risks is often a topic discussed at product-specific advisory committee meetings. 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."	We believe that FDA's benefit-risk framework could be a useful tool to maintain a focus on the medical and scientific issues discussed at advisory committee meetings. The framework could also serve to anchor the committee in all the factors that will be addressed by FDA when the final regulatory decision is made. We encourage FDA to develop a plan to implement the benefit-risk framework during advisory committee meetings in the near future where appropriate.
III. IMPORTANT CONSIDERATIONS FOR FDA'S PREMARKET BENEFIT-RISK ASSESSMENT OF DRUGS AND BIOLOGICS		
A. Overview of Important Considerations		
	This section refers to the FDA's Benefit-Risk-Framework for New Drug Review (Figure 1.).	To improve the general flow of the document and the immediate understanding of the reader, suggest referring specifically to the 'Evidence and Uncertainties' column of Figure 1.
	The value of this section would be enhanced if additional illustrative examples using the sBR framework with different types of data was added.	BIO suggests adding reference to particularly illustrative example of FDA and Sponsor using the SBR framework for different types of data.
Table 1:	Table could have more in-depth information.	Table 1 only includes examples of important considerations. However, the benefit-risk framework has specific prompts for reviewers that could provide better insight to sponsors as well.

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Table 1		The elements outlined in Section IIIC (Line 284, The Role of Patient Experience Data in FDA's Benefit-Risk Assessment) should be reflected in Table 1. For example, we suggest including: perspective reflected on (1) impact of disease in Analysis of Condition; (2) available treatments under Current Treatment Options; (3) benefits most meaningful in Benefit; and (4) patient preference and willingness to tolerate risks/uncertainties under Risk and Risk Management. For the Conclusions Regarding Benefit-Risk row, the Important Considerations column mentions considering individual patient perspectives. It is not clear why individual patient perspectives are only mentioned in this row and not in other rows/Dimensions of the framework. The consideration of individual perspectives should be incorporated consistently for each element within the benefit-risk framework.
Table 1. Examples of Important Considerations for each dimension of B/R framework	We commend FDA for providing a thorough list of important considerations for each dimension of the Agency's pre-market benefit-risk assessment. However, this section could be improved by explicitly identifying the ways that patient experience data and patient preference information could be considered as an input in each dimension.	We recommend that the Agency update Table 1 to include, in each dimension, the ways in which patient experience data or patient preference information could be included in each section.
Table 1, page 8 Current Treatment Options:	The "Current Treatment Options" row of the benefit-risk framework includes the following bullet as an important consideration for FDA: "Efficacy and safety of other interventions used for the intended patient population, such as drugs used off-label or other nondrug interventions."	FDA should expand its discussion of the therapeutic context in this guidance to better explain why the agency takes a broad view of the treatment armamentarium when assessing the therapeutic context. This is described beginning on line 135 where the agency discusses the therapeutic context as an important consideration in understanding the unmet medical need in a particular therapeutic area. However, in stating explicitly in the benefit-risk framework that FDA considers the

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	This statement could benefit from additional explanation regarding how such information would be factored into FDA's regulatory decision-making.	efficacy and safety of approved, off-label, and nondrug interventions, it would be helpful if the agency acknowledged that these considerations are not for purposes of any comparative assessment of safety and efficacy that would be the basis for FDA's regulatory decision. Rather, the purpose of this assessment of other therapies is to assess the extent of unmet medical need, regardless of any new drug under FDA review.
Table 1, page 8 Current Treatment Options:	All current approved treatments may not be available to patients for varying reasons resulting in the inability of patients to start or continue a treatment and the need for additional treatment options.	We suggest adding a bullet under "Important Considerations" for "Current Treatment Options" stating: "Understanding of limitations in supply and product access of current approved treatments."
Table 1, page 8 Benefit	Another example of an important consideration for benefit is doing preparation, especially with respect to the intended patient population, specifically what dosing preparation is feasible and encourages compliance.	We suggest editing this bullet to read: "Important characteristics of the drug (e.g., a less burdensome dosing regimen, dosing preparation or route of administration)"
Table 1, page 8 Benefit	The Draft Guidance states, "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)."	Additional guidance regarding how the FDA prefers the heterogeneity in treatment effects to be communicated (e.g., statistical tables, graphs, text) would be helpful.
Table 1, page 8 Benefit	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)	It would be helpful for the Guidance to include whether the Agency suggests any particular displays or summaries to describe the distribution of treatment effects.

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Table 1, page 8 Benefit	The wording "uncertainty (e.g., a confidence interval)" may imply that the document only focuses on the uncertainty due to chance not the uncertainty due to potential bias.	BIO suggests including wording to discuss uncertainty due to potential bias.
Table 1, page 9 Risk and Risk Management:	The table discusses the benefit-risk framework dimension of risk and risk management.	BIO suggests this section also mention population subgroups e.g., define specific subpopulations with greater or lesser risks of treatment which could impact the benefit-risk assessment in these patients. Additionally, we suggest adding a bullet to address subgroups. For example: • Ability to identify subpopulations for whom the benefit-risk profile may differ from that of the rest of the study population.
Table 1, page 9 Risk and Risk Management:	The Draft Guidance states, "Level of certainty for a causal association between drug exposure and risk" More guidance is needed on how FDA will evaluate level of uncertainty for a causal association. This statement is too subjective.	This calls in to question how theoretical risk will be managed for gene therapy products. When considering the benefit-risk for gene therapy products, FDA should think more about weight of evidence from the causal relationship. FDA should clarify that theoretical risks don't adversely impact the benefit risk assessment. Such risks can be accounted for risk in the post market considerations.
Table 1, page 9 Risk and Risk Management:	The considerations provided regarding adverse events and safety signals do not capture importance of symptomatic adverse events (AEs), tolerability, or risk from the patient perspective. We note that even mild-moderate symptomatic AEs can have a significant impact on patient health-related quality of life and adherence to treatment. We encourage FDA to update this section to reflect this consideration, as was done in FDA's 2019 Discussion	We suggest FDA add the following bullets to this section: • "Adverse effects (e.g., nausea) that could affect tolerability or adherence. • Available data on previously approved risk mitigation measure effectiveness in the same patient populations, disease states, or therapeutic area."

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	Document on Benefit-Risk Assessment Throughout the Drug Lifecycle.[9]	
Table 1, page 9 Conclusions Regarding Benefit-Risk:	The Draft Guidance states, "Overall conclusions about the quality and strength of evidence and the remaining uncertainties regarding benefits and risks."	It would be helpful to have a better understanding regarding the types of uncertainties that would most likely impact regulatory decision making.
Table 1, page 9 Conclusions Regarding Benefit-Risk:	Additional clarification is needed regarding what is meant by "relative importance of the benefits and risks in the overall indicated population, but also considering individual patient perspectives". A discrete choice experiment, for example, is conducted at the population level, though confidence intervals show variation in relative importance. By "individual patient perspectives", is patient testimonies meant?	Additional clarification is requested.
Table 1, page 9 Conclusions Regarding Benefit-Risk:	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)	BIO suggests deleting the word serious. Further, we suggest providing guidance on how this association between benefit and adverse events could be assessed (e.g., using longitudinal heat map). The association between meaningful benefit and non-serious events may also be relevant.
B. The Impact of Uncertainty on Benefit-Risk Assessment		
	This is a good place to discuss uncertainty associated with confounding and bias, which is lacking in the document.	We suggest addressing potential confounding and bias issues.

[9] "Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document" US Food and Drug Administration. May 3, 2019.

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	An additional bullet should be added concerning theoretical risks that are not observed in trials	FDA should clarify that theoretical risks don't adversely impact the benefit risk assessment. Such risks can be accounted for risk in the post market considerations.
Lines 225-256:	This section omits some of the important aspects of uncertainty that should be included in FDA's bulleted list.	We recommend adding the following items to FDA's bulleted list of uncertainties: • treatment effects that are marginal statistically or where the clinical meaningfulness of the effect is uncertain • discordance in treatment effect between endpoints or trials • differences in safety profiles between trials • long-term safety and efficacy
Lines 236-238:	The Draft Guidance states, "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."	BIO suggests rephrasing this bullet because while they are important considerations, it is unclear how these considerations are affecting benefit-risk review.
Lines 255-256:	The Draft Guidance states "Introduction of a novel technology or control strategy in the drug's manufacturing process, or other potential issues regarding the product formulation or manufacturing."	We ask the Agency to clarify what is meant with respect to risk assessment for chemistry and manufacturing controls. These are normally assessed within the context of the Module 3 and confirmed during routine inspections. Furthermore, for drug-device combinations, methods like Human Factor Studies help frame risk-benefit. As such, the inclusion of language regarding chemistry and manufacturing controls may be confusing, since this is addressed elsewhere.
Lines 280-283:	The Draft Guidance states, "Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features	To ensure consistency across relevant Guidances, we suggest editing the text of this Guidance to read: "Patient contribution is optimized in small sample size studies by minimizing bias and

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	such as randomization, blinding, enrichment procedures, and adequate trial duration." We appreciate the recognition of small sample sizes in rare diseases and agree with the Agency that it is important to maximize the potential for clinical trials to provide interpretable scientific evidence. However, the current language implies that randomized, blinded trials are the only way to achieve this objective. We note that this implication is not consistent with prior regulatory guidance. For instance, FDA has also noted in their draft guidance on Rare Diseases: Common Issues in Drug Development[10] that "In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials." Additionally, FDA's Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products[11] states that: "While a randomized placebo-controlled trial can provide more definitive evidence of a small treatment effect than any other kind of trial of the same size, there are instances when this design and other concurrently controlled superiority designs may not be feasible or ethical." Given the investments made in advancing innovative approaches under PDUFA VI (e.g., real-world evidence,	maximizing precision with trial design features. Where appropriate, studies should utilize features such as randomization, blinding, enrichment procedures, and adequate trial duration. However, there may be certain cases (e.g., rare disease, gene therapy) where all these features may not be ethical or feasible."

[10] "Rare Diseases: Common Issues in Drug Development" FDA Draft Guidance for Industry. FDA CDER & CBER. January 2019.
[11] "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" FDA Draft Guidance for Industry. FDA CDER & CBER. December 2019.

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	complex innovative designs, model-informed drug development), we suggest that FDA revise the language here to reflect that there are options beyond the randomized controlled trial for generating evidence to support benefit-risk assessments.	
C. The Role of Patient Experience Data in FDA's Benefit-Risk Assessment		
General Comment:		Additional considerations should be given to integrating many types of PED (e.g., qualitative input, PRO data, RWE data, and PPI) into the overall B-R Framework. These PED provide insights into the impact of disease, unmet medical needs, patient treatment preferences, and willingness to accept risks.
Line 284:	We appreciate this section on how PED can inform the different aspects of the benefit-risk assessment. However, we believe that the importance of PED should be acknowledged early in this guidance and consistently referred to throughout.	We recommend that these examples be incorporated into *Table 1: Examples of Important Considerations for FDA's Premarket Benefit-Risk Assessment of NDAs, BLAs, and Efficacy Supplements*. The opening remarks on the importance of PED could be moved to the section on Regulatory Background.
Lines 297-298:	In this section, FDA describes in bullet format various aspects of the benefit-risk assessment that can be informed by patient experience data. After describing several bullets regarding the therapeutic context, FDA includes the following bullets: • Potential benefits that are most meaningful Acceptability of risk and uncertainty	Both of these examples of patient experience data can inform FDA's benefit-risk assessment because of their relation to the therapeutic context. The patients' assessment of the impact of disease informs the benefits that are most meaningful to patients and the patients' acceptability of risk. Similarly, the patients' assessment of the unmet medical need also informs the acceptability of risk. Disease severity and extent of unmet medical need should correlate with patients' (and FDA's) acceptability of risk. It would be helpful if the guidance clearly articulated the linkage between lines 297-298 and the therapeutic context.

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Line 288:	The Draft Guidance states, "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…" We recommend that FDA consider adding a point regarding including caregiver/family input which may be particularly important in settings where patients cannot self-report.	As such, we suggest editing the text to read: "Patients are experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcomes of medical treatment. In populations where patients cannot self-report (e.g., in some pediatric indications or in patients with cognitive impairment), caregiver and family input can provide important insights into the lived experience of the disease. Patient experience data can inform nearly every aspect of FDA's benefit-risk assessment throughout the drug lifecycle…"
Lines 302 – 305:	The Draft Guidance states, "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."	We appreciate FDA's ongoing efforts to communicate how PED is used to inform their review using the PED Table. However, we note that the use of this table is inconsistent throughout the Agency, leaving Sponsors, patients and other stakeholders with an unclear view of how PED can inform regulatory thinking. We encourage the FDA to adopt the recommendations developed by BIO's Patient-focused drug development task force.[12]
Lines 307 – 315:	The Draft Guidance states, "...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	We appreciate FDA's intent but note that this perspective does not allow for informed treatment decisions by patients/providers. For example, some patients may be willing to accept a drug with significant risk if the drug is more tolerable than available treatment options. Further, the totality of evidence should not be ignored. Other types of data should be considered. Therefore, we suggest that FDA consider describing how benefits and risks can be presented in a way to allow informed treatment decisions when patient preference data or other PED

[12] "BIO White paper of FDA's Statement of Patient Experience." Biotechnology Innovation Organization Patient-Focused Drug Development Taskforce. 2021.

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	individuals who might benefit through the use of predictive biomarkers or other means."	demonstrates that some patients are willing to accept certain risks.
Line 313:	The Draft guidance states, "...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."	We suggest that this section be revised to indicate that baseline measurements of how patients feel, or function could also be used to identify patients who might benefit most from treatment. As such, we suggest editing the text to read: "...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, baseline clinical outcome assessments (e.g., cognitive or functional assessments), or other means."
IV. ACTIVITIES THAT OCCUR IN PREMARKET DEVELOPMENT THAT INFORM BENEFIT-RISK ASSESSMENT		
Lines 318-574:	This section of the Guidance includes a number of lists of considerations and examples.	The inclusion of additional guidance on these considerations, and methods and references to more detailed visual tools, case studies and lessons learned would be beneficial.
Line 324:	The Draft Guidance seems to only mention defining the overall population. In fact, defining subpopulations in which the benefit-risk assessment will be performed is also important and should be discussed.	We recommend adding examples of subpopulations and a discussion of defining subpopulations.
Line 341:	The Draft Guidance states, "reducing important uncertainties."	We suggest clearly stating minimizing chance findings and potential biases.
A. Structured Benefit-Risk Planning During Drug Development		

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Line 340-345:	As one of the tools in benefit-risk planning, the agency suggests limiting the indication to patients failing available therapies. It is important to note that available therapies may have benefit-risk inferior to that of a new therapy, which may be more tolerable, easier to administer, etc.	We suggest that the Agency address their view and approaches to comparing benefit-risk profiles between new and established products in situations where patients are not failing available therapy but would benefit from a safer product. Patients who are not failing therapy should be able to benefit from innovations that improve safety.
Lines 376-378:	The Draft Guidance states, "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."	FDA should clarify that use of an active control does not imply that any direct comparison between the benefit-risk profiles is necessary for FDA's approval. Furthermore, FDA should state that such a consideration acknowledges existing uncertainty regarding the benefits and risks of the new drug and permits better planning to address the uncertainty through trial design considerations. FDA should also further elaborate that this could be a discussion topic at the EOP2 meeting when planning for the registrational trials is discussed. This would give sponsors greater clarity on FDA's current thinking on the benefit-risk assessment of the new drug. Further, it would be helpful if the Guidance included thresholds of acceptable data and examples of such scenarios.
B. Appropriate Interactions Between a Sponsor and FDA During Drug Development To Inform Benefit-Risk Planning		
Lines 406-437:	FDA has consistently promoted the value of early FDA-Sponsor interactions; however, there can be challenges for FDA and Sponsors to schedule these meetings to include the right expertise in a timely and efficient manner. In addition, different types of B/R data may require different approaches, and therefore different expertise and timing. In particular, for development programs that are incorporating patient preference	We suggest FDA include: • additional granularity, potentially with case examples of when to meet, and who to include depending on the type of data (e.g., Patient Preference Information, PROs, Clinical data, etc.) and expertise required and how to provide available information and data to the Agency.

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	information, the optimal time to meet may not align well with the traditional milestone meetings or may need additional more focused meetings with shorter turn around. Therefore, it would be valuable for FDA to provide additional granularity, potentially with case examples of when to meet, and who to include depending on the type of data and expertise required.	guidance on the role of the future type D meetings for B-R related planning discussions.
Lines 425 – 427:	The Draft Guidance states, "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."	We encourage FDA to provide flexibility for rare diseases, (e.g., when open-label study design or the lack of a comparator arm cannot be avoided). As such, we suggest editing the text to read: "They could also involve considerations on the most appropriate trial ~~best~~ design or approach to leverage available interpretable scientific data (e.g., from registries, natural history data) to characterize benefits and risks where the population is limited or vulnerable, such as for rare or serious diseases or pediatric populations."
Lines 430-436:	The language is vague concerning sponsors proposing a question or agenda item during EOP2 meetings.	It would be helpful if FDA included examples of meaningful questions that would elicit quality feedback and include more explanation on what FDA envisions the discussion to look like.
C. Collecting Patient Experience Data During Development to Inform Benefit-Risk Assessment		
		The collection of PED to inform benefit-risk assessment is outlined in this section. However, it would be helpful if this were integrated into Table 1, especially if it is to be reflected in the package insert.
Line 458:	The Draft Guidance states, "Collecting robust patient input on the symptoms or other aspects of their condition that matter most to patients can inform and	We suggest adding examples of acceptable methods of collecting patient experience data, similar to the footnote on patient preference information.

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	strengthen the rationale for the endpoint selection and development of COAs."	As such, we suggest editing the text to read: "Collecting robust patient input (e.g., through qualitative, quantitative, or mixed methods) 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."
Line 468:	The Draft Guidance discusses use of PPI.	Additional discussion regarding approach or timing of interactions between the sponsor and FDA about patient preference information for benefit-risk assessments would be helpful to ensure Sponsors come to FDA at the right time with the right information.
Lines 475-478:	A regulatory submission requires a PPI be collected through a formal study with pre-specified protocols and analysis plans and include a broad and representative sample of patients.	The Guidance is not clear on where patient experience data will be captured in the drug label i.e., in a 'patient experience' section in the study protocol or standalone protocol/study for patient preference only. BIO requests FDA clarify their expectation. The Guidance is not clear on if patient preference outcomes should be collected with other PRO endpoints. BIO requests preference outcomes be collected with PRO endpoints so as to not add to patient burden.
D. Conducting Additional Analyses to Inform Benefit-Risk Assessment		
Lines 490-491:	The Agency refers to *"…significant or novel uncertainties regarding the drug's benefits and risks*"	Propose that the Agency clarify what is meant by "*significant or novel*" uncertainties. An example of each type of uncertainty would be helpful.
Lines 507-508:	The Draft Guidance includes analyses combining benefits and risks in a combined analysis and/or incorporating information about desirability of outcomes and tradeoffs between benefits and risks. However, it is not clear whether the "desirability of outcomes and tradeoffs between benefits and risks" should use the perspective of the patient rather than, for example, the perspective of a physician or the general public.	BIO recommends revising this statement to read, "..,desirability of outcomes to patients and the tradeoffs patients are willing to make between benefits and risks."

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Lines 507-508:	The Draft Guidance states, "Integrating benefits and risks in a combined analysis and/or incorporating information about desirability of outcomes and tradeoffs between benefits and risks."	We suggest providing guidance on whether particular methods (e.g., multi-criteria decision analysis) are recommended. Further, it is unclear whether the guidance is referring to trade-offs from a patient preference perspective, or from the Agency's perceptive. We believe this statement should allow for incorporating the perspectives of multiple stakeholders including patients. As such, clarification is requested.
Lines 510-514:	The Draft Guidance states: "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."	We request that the FDA elaborate how to best bring these topics to the table, in which types of meetings or interactions and how to ensure the relevant people from FDA review division are present for those interactions to obtain feedback. Having clear guidance or suggestions here could encourage sponsors to raise the topic of patient experience data and other additional information collection in earlier interactions. We request that FDA include examples.
Lines 510-519:	That Agency references situations where additional analyses may add value can be anticipated early in development,	Examples and recommendations on the quantitative methodologies for the additional analyses would be helpful.
Lines 521-524:	FDA references a lengthy list of potential quantitative methods without prescribing a specific method – and suggests the appropriate method depends on the available data. Some methods included in the list do not capture the patient perspective on benefits and risk.	We agree that FDA does not need to prescribe which specific quantitative methods are acceptable, and we agree that the selection of the appropriate method depends upon many factors, including available data, preference sensitive nature of the decision, residual uncertainties, etc. We recommend that, even though the Agency does not wish to prescribe specific approaches, the Agency provide clarification

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		as to the types of methods that likely will be best suited to addressing certain types of questions. For example, the Draft Guidance references Mt-Isa et al (2015) which identified approximately 50 methods. We recommend that the Agency provide clarification as to what subset of QBR methods in the reference provided are informative for regulatory decision making.
Lines 524-526:	The Draft Guidance states, "The interpretability and usefulness of results rests on the validity and assumption of the selected method and underlying data, both of which should be fully reviewable by the Agency." It is unclear what is meant by "fully reviewable by the Agency" Would this be in the form of a (supplemental) statistical analysis plan, or review at a formal meeting with FDA, as described in Section B?	BIO suggests the Guidance include additional information on expectations of when and how the Agency would like to review these types of methodologies / analyses as they would be built into a development program / study, including examples.
E. Presenting Benefit-Risk Considerations in the Marketing Application		
	General comment on section	FDA should be consistent throughout with what they want to see and how they want to see it. It would be helpful to have more specificity regarding when information would be most impactful and when is best to use data to inform B/R decision making.
Lines 538-541:	The Draft Guidance states: "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"…	It would be helpful for the Guidance to include recommendations on how patients' voice/ input can be translated into science, submissions and labeling claims in a way that is relevant and valuable for FDA review process.

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Lines 539-541:	The Draft Guidance states, "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))."	We suggest addressing whether FDA's definition of "integrated" summary includes an overall qualitative assessment or can include an overall quantitative assessment.
Lines 549 – 552:	The Draft Guidance states, "Discussion of the magnitudes of effects and treatment effects (difference between drug and comparator)...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."	We suggest adding details to keep the wording and descriptions consistent with FDA's PFDD guidances and discussion documents. We recommend editing the text to read: "Discussion of the magnitudes of effects and treatment effects (difference between drug and comparator) with pre-specified thresholds and methods...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~~ or between-group effect in the population." It would also be helpful to provide the rationale for this analysis here. More discussion with references would be helpful.
Lines 562-563:	Presentation of a graphical or tabular summary of results for the most important benefits side by side or juxtaposed with important potential risks	The BRAT framework is an especially effective model for benefit-risk assessment. It would be helpful if the guidance had a good bibliography that might point the way to things like BRAT. A good example is the presentation of benefit-risk through value trees, key B/R tables, and forest plots. Further, in the EU and several other jurisdictions, the term important potential risk has a regulatory definition in the risk management plan. This term is not defined in the US post-

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		market regulations or REMS. Hence, we recommend deletion of the term "potential" to avoid any confusion.
V. BENEFIT-RISK ASSESSMENT CONDUCTED IN THE POSTMARKET SETTING		
Lines 583-588:	The Draft Guidance states "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."	BIO suggests adding "patient experience data" to types of postmarket evidence.