ISPE's official response to the U.S. Food and Drug Administration's (FDA) draft guidance for industry on Benefit-Risk Assessment for New Drug and Biological Products, endorsed November 24, 2021

| Type of Comment | Section | Line | BRACE SIG & ISPE Member Comments |
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| | Preamble to comments | Intro to Comments | The FDA Draft Guidance entitled "Benefit-Risk Assessment for New Drug and Biological Products" represents an important advance in FDA's thinking regarding how to incorporate patient experience and patient preferences into the benefit-risk assessment of new drugs and biologics. The guidance emphasizes the role of patient experience data, and how to collect patient experience data during development to inform benefit-risk assessment. ISPE commends the FDA for the release of this new draft guidance. ISPE respectfully submits these comments and suggestions for the FDA consideration as the draft guidance is revised. Please note that ISPE BRACE SIG members who are employees of EMA or members of a committee or working party of EMA have excluded themselves from contributing, reviewing or supporting these comments submitted by the ISPE BRACE SIG. |
| Minor | II | 135,147, 152 | 1. FDA to further emphasize the importance of sponsors' undertaking a rigorous approach to presenting the therapeutic context, the B-R evidence generated to date, and the Uncertainties when developing a structured benefit-risk assessment. |
| Major | III, A | 223-224 | 2. The FDA Draft Guidance entitled "Benefit-Risk Assessment for New Drug and Biological Products" represents an important advance in FDA's thinking regarding how to incorporate patient experience and patient preferences into the benefit-risk assessment of new drugs and biologics. The guidance emphasizes the role of patient experience data, and how to collect patient experience data during development to inform benefit-risk assessment. ISPE commends the FDA for the release of this new draft guidance. ISPE respectfully submits these comments and suggestions for the FDA consideration as the draft guidance is revised. Please note that ISPE BRACE SIG members who are employees of EMA or members of a committee or working party of EMA have excluded themselves from contributing, reviewing or supporting these comments submitted by the ISPE BRACE SIG. |
| Major | III, C | Sentence beginning on Line 313 | 3. Could the FDA provide more detail as to how (i.e., approaches and mechanisms used) the FDA carefully weighs and considers the patient perspective. |
| Major | IV, C | 439-481 | It is important that FDA benefit risk assessments using PED and PPI are conducted consistently within and across Divisions and that the process is robust and transparent to Sponsors and patients. To meet this important objective, we support: 1) the development of internal FDA policies and procedures that promotes the rigorous, consistent, predictable and timely review of patient preference and patient experience data, 2) the development and implementation of 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. |
| Major | IV, C | Lines 442-450 | Could FDA please be more explicit as what is the minimum standard for inclusion of patient experience data in structured benefit-risk assessments in order for such data to be 'considered' or 'accepted' by the FDA. In addition, could the FDA be more specific as to how (i.e., what methods) should be used to capture such patient experience data and what mechanisms should be evident to show that bias has not contaminated data. |
| Major | IV, C | Lines 454-455 | FDA is urged to produce methodological guidances as soon as possible on the development and use of systematic approaches to better incorporate the patients' voice into drug development and evaluation. |
| Major | IV, D | 486-532 | The first sentence in Section IV D (Conducting Additional Analyses to Inform Benefit-Risk Assessment) states, "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." This statement is vague, specifically with regard to whose judgments the Agency is referring to and why the judgment must necessarily be qualitative or subjective. FDA recently used structured, quantitative methods in its own (Lackey et al., Circulation 2021;144:655–658.) Therefore, we propose that the Agency replace the word "inevitably" with "often" and indicate that there may be cases in which benefit-risk assessment can be conducted using quantitative methods. |

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| Major | IV, E | 534-574 | We agree that FDA does not need to prescribe which specific quantitative methods are acceptable, and we agree the selection of the appropriate method depends upon the available data. Currently, the draft guidance references Mt-Isa et al (2015) which identified approximately 50 methods; however, we recommend that the Agency provide clarification as to which of these methods are likely to be useful in benefit-risk assessment and which are not. It would be valuable for the Agency to clarify what types of methods are likely to be best suited for addressing certain types of questions and whether all are equally acceptable to the FDA as part of the marketing application submission. We could give FDA direction here by providing the types of methods that we deem as high value, e.g., multi-criteria decision analysis (MDCA), stochastic multicriteria acceptability analysis (SMAA) and NCB. |
| Minor | IV, E | 562-567 | Could FDA please provide a list of key sources in the published literature on how to present a comprehensive structured benefit-risk assessment for interested readers? |
| Major | V | 596-601 | Could FDA provide further detail regarding how it would incorporate new information obtained via evaluating a product's REMS program into its structured benefit-risk assessment? In many instances, REMS evaluations yield results that are equivocal in some way. How does the Agency view such data and use it to assess whether the product's benefit-risk profile has changed? |