November 13, 2017

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

Re: Docket No. FDA-2017-N-4076: Benefit-Risk Assessments in Drug Regulatory Decision-Making; Public Meeting; Request for Comments

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Benefit-Risk Assessments in Drug Regulatory Decision-Making."

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.

General Comments:

BIO believes that the benefit-risk framework represents an important advancement in FDA product regulation because it reflects and reinforces the underlying reality that the FDA review process is grounded in the assessment of both benefits and risks. In addition to providing a framework for the evaluation of benefits and risks, the FDA's introduction and implementation of the structured benefit-risk framework has helped improve the transparency and communication of FDA's decisions on approvals of new therapies, including clinically meaningful efficacy and safety information most relevant to FDA's regulatory decision making. The framework has also allowed the FDA to share important information with the public about what to expect from approved therapies.

BIO supports FDA's continued efforts to evaluate and improve the clarity of this complex and critical process of benefit-risk assessment throughout the lifecycle of drug evaluation. While the FDA benefit-risk framework has provided increased transparency and communication, additional work is needed in order to continue to advance and improve upon the current FDA benefit-risk framework. Please find below, recommendations for areas to continue to enhance the FDA's benefit-risk framework.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

Increased Transparency and Flexibility of Benefit-Risk Assessment in Complete Response Letters:

As mentioned above, BIO commends the FDA for using the benefit-risk framework to increase transparency and communication of FDA's decisions on approved new therapies. However, equally important is the provision to sponsors of FDA's fully populated, benefit-risk grid for entities that are not approved and that receive a complete response letter (CRL). For CRLs, the Agency's benefit-risk grid assessment can be critical in helping the sponsor to address and overcome issues that prevented drug approval. The grid also helps elucidate how the FDA views the product in its totality and not just the issue(s) that led to the complete response.

In addition, we agree with the Eastern Research Group's recommendation that the benefit-risk framework for approved products be posted as a stand-alone document. Currently, the benefit-risk framework posting is not easily located on the FDA website. As part of the goal is to communicate this information, we recommend that the FDA link from other sections, such as the Drug Trials Snapshots page or Novel Drug Approvals page.

BIO also requests that the FDA consider incorporating other key graphics such as effect tables and value trees into the benefit-risk framework process, moving forward. The European Medicines Agency currently requires rapporteurs to develop an effects table during review of a product and the table is eventually made available to the public. Public availability of such graphics will aid the FDA in providing important information about approved products to the public.

Consistent Use of the Benefit-Risk Assessment Across Review Divisions:

BIO encourages FDA to implement 'best practices' for benefit-risk assessments across the FDA to ensure that within and across review divisions, FDA staff is informed about approaches to structured benefit-risk assessments. 'Best practices' for benefit-risk assessments will allow for a more consistent, transparent, and efficient evaluation of the benefits and risks of all FDA regulated products. Relatedly, it would be important to educate FDA staff about how to incorporate the patient perspective in benefit-risk assessments. This is especially important for review divisions that oversee rare [serious and unmet medical needs] diseases, and where review divisions may not be experienced with such assessments in small patient populations. BIO also requests that the FDA consider other mechanisms that will encourage consistency in how FDA reviewers are applying the benefit-risk framework within and across review divisions.

Benefit-Risk and the Patient Perspectives:

BIO commends the FDA Plan for Issuance of Patient-Focused Drug Development Guidance (May 2017) under 21st Century Cures Act Section 3002. These guidance documents will be important for informing sponsors, patient organizations, academic

researchers, and expert practitioners of the FDA's expectations for collection, submission, and utilization of patient experience data. As the FDA begins drafting these guidance documents, we ask that the FDA consider:

- Providing clarity on FDA's expectations and standards for reflecting inclusion of patient preference information and patient reported outcomes in the label of drug products. For example, the recent (June 2017) inclusion of such information in the Rituxan-Hycela label is laudable, however, more information from FDA on expectations for gaining inclusions of such information in labeling would be helpful to all industry sponsors moving forward. We recommend that, as FDA coordinates public meetings under 21st Century Cures/PDUFA VI to define the framework for patient-focused drug development, it request input on how patient-focused drug development can and should contribute to the benefit-risk assessment framework.

- Providing more information about the stages during the drug review and approval process when patient experience information may impact the FDA's benefit-risk assessments as well as when these data should be submitted to the FDA for inclusion in such assessments. Additionally, it is important that guidance specify when and how sponsors can consult with the FDA during the pre-submission period regarding the conduct of patient preference studies.

- Including a section in the FDA benefit risk-framework that discusses, patient experience data and related information that FDA considered in its regulatory decision making and in its benefit-risk assessment.

- Continuing to identify opportunities to use patient centric information to inform the FDA thinking regarding the level of patient tolerance for risks and patient perspectives of the benefits of particular products. Currently, patient centric information is used primarily to support the general understanding of the burden of disease but patient perspective information has the potential to inform other aspects of drug development and review. The FDA should consider opportunities for the use of patient perspectives beyond burden of disease. We recommend that as FDA coordinates public meetings under 21st Century Cures/PDUFA VI to define the framework for patient-focused dug development, FDA specifically request input on how patient-focused drug development can and should contribute to the benefit-risk assessment framework.

- Providing more information about how the FDA may handle certain situations, such as, when, for example, a pivotal trial fails to demonstrate efficacy on a primary endpoint but is successful in demonstrating efficacy on a secondary endpoint and results of a patient preference study suggest that patients are willing to accept the product's risks in exchange for the secondary endpoint benefit.

- The challenges for sponsors working with small patient populations when considering how to provide patient perspective information. Quantitative patient assessments may not be necessary or feasible for products developed for rare disease due to the small size of the patient populations and high unmet needs. BIO asks that the FDA

be receptive to a variety of methodological approaches, including both qualitative and quantitative, for collecting such information for products under development for limited populations.

Conclusion:

Thank you for the opportunity to present our views on the implementation of the FDA's structured benefit-risk framework. BIO and BIO's member companies look forward to collaborating with FDA and other stakeholders to build on the success of the benefit-risk framework. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization