Biotechnology Innovation Organization

May 31, 2018

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

Re: Docket No. FDA-2018-N-1010: Food and Drug Administration Prescription Drug User Fee Act VI Benefit-Risk Implementation Plan.

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 Prescription Drug User Fee Act VI Benefit-Risk Implementation Plan.

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 members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

General Comments:
BIO supports the FDA's continued efforts to evaluate and improve upon the clarity of the complex and critical process of benefit-risk assessment (B/R assessment) throughout the lifecycle of drug evaluation. While BIO commends the FDA for the great progress in implementing the benefit-risk framework (B/R framework), especially as it relates to transparency and communication of benefit-risk assessments (B/R assessment), additional work is needed to continue to advance and improve upon the current FDA B/R framework. In order to continue to advance the science of B/R assessments and the ability of the framework to inform regulatory decision making, BIO believes that there should be increased emphasis and guidance on the utilization of the B/R framework as a decision support tool, implemented earlier in development, rather than just to support communication following a regulatory decision. For example, the FDA has identified additional opportunities to advance their B/R work, through: (1) incorporation of patient experience into drug development, evaluation, and review and (2) exploration of more quantitative approaches to inform B/R assessments in targeted cases, we ask that these efforts be highlighted as steps toward using the B/R framework as a decision support tool.

As the B/R framework relates to patient experience data, BIO believes that clear guidelines regarding how the FDA will synthesize information, how review division will utilize this information at the reviewer level, and how this process will be systematically implemented across the agency would be beneficial to all stakeholders. Specifically, we ask the FDA to clarify how they will incorporate patient perspective into the B/R assessment. It will be important for the FDA to provide information regarding how the Agency expects to use patient engagement meetings, real world data, and patient experiences in their understanding of what risks are acceptable to patients.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

Additionally, further emphasis should be placed on defining the methodology to develop the B/R assessment, which could include implementing consistent definitions and tools (both qualitative and quantitative) for FDA reviewers to use when assessing medical products. BIO also suggests that this be done, to the extent possible, in alignment with other international regulatory authorities, including the European Medicines Agency.[1] Such standardized definitions could assist FDA reviewers in answering questions such as how to define an important benefit, how to define an important risk, how to determine in which situations risk minimization or pharmacovigilance activities are required to further mitigate or characterize a risk, measuring a patient's risk tolerance, and how B/R assessments inform the indication for which the product is ultimately approved. Such activities could include a methods tool kit or catalog with case studies, standards for methods application, information regarding the adaptation and application to post-marketing assessments, as well as information regarding use of quantitative B/R assessment approaches. In the B/R implementation plan, we encourage FDA to clearly outline how they plan to advance and define the specific methodology for developing B/R assessments at FDA, for example, as part of the decision-making context. In addition to implementing consistent definitions and tools for FDA reviewers, BIO asks the FDA to consider updating its Manual of Policies and Procedures and providing training to reviewers to ensure consistent methodology and approaches to B/R assessment across therapeutic areas, Divisions, and Centers.

Communication around the B/R Assessment and the B/R Framework:
BIO applauds FDA for its strides to more clearly communicate the B/R framework with all stakeholders. In order to continue to advance these efforts, BIO encourages the FDA to consider developing a mechanism that allows for easier location of B/R information on the FDA's website by either flagging or linking to the B/R assessment in FDA review documents. Additionally, as it currently stands, the B/R assessment grid in FDA reviews is followed by a tabular listing of what patient experience data was included in the marketing application, and where it is located. Moving forward, BIO believes that the patient experience data that influenced the B/R grid should to be integrated, or cross-referenced, and made more accessible for patients and providers.

BIO also asks the FDA to consider using structured B/R assessments routinely within the framework of product-specific Advisory Committees. For example, BIO encourages the FDA to include the B/R framework, developed in collaboration with or in addition to a B/R framework developed by the Sponsor, in Advisory Committees briefing materials, rather than waiting until the end of the FDA's review. We believe that Including the B/R assessments in the Advisory Committee briefing materials may help lead discussion during the Advisory Committee meetings.

Finally, we also ask the FDA to consider moving from a post-approval summary of B/R considerations to a more active use of a specific B/R framework throughout drug development. To this end, the FDA could engage with sponsors during IND or pre-NDA/BLA milestone meetings and allow for discussion of the B/R assessment at other set time points.

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[1] European Medicines Agency Benefit-Risk Methodology.

Such a discussion would benefit both the FDA and Sponsors when deciding whether to advance a particular compound into later stage development.

BIO appreciates this opportunity to submit comments regarding FDA's Prescription Drug User Fee Act VI Benefit-Risk Implementation Plan; we would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND ON THE FDA'S BENEFIT-RISK FRAMEWORK		
Page 3	The goals of the framework outlined on page 3 focus on communicating the rationale for a particular B/R decision, but there is not an emphasis on the framework supporting the decision making process.	BIO requests that the FDA indicate in this section that in addition to serving as a communication tool, the B/R framework also supports regulatory decision making.
III. PROGRESS MADE ON PDUFA V ON BENEFIT RISK ASSESSMENT		
Develop and Publish a Five-Year Plan that Describes FDA's Approach to Implementing Structured Benefit-Risk Assessment in the New Drug Approval Process		
Revise Review and Decision Memo Templates and Manuals to Incorporate FDA's Approach to Benefit-Risk Assessment		
Page 4	This section indicates that CBER and CDER adopted slightly different approaches to implementing the B/R framework into the review process.	BIO recommends that the plan also include a provision to ensure that the learnings gained by CBER in using patient experience data and incorporating patient experience data into its assessment process will be shared with CDER and the public. Furthermore, BIO recommends that the B/R framework also be used for sponsor interactions with CDRH for combination products whose primary mode of action is drug or biologic.
Train Review and Management Staff on the Revised Templates and Manuals		
Page 5	As outlined above, to support more consistent use of the B/R assessment across centers and review divisions, training should be provided to review staff.	BIO requests that CBER and CDER Biostatistics & Epidemiology staff receive training on the fundamental and advanced principles of B/R assessment, including a range of preferred quantitative tools (especially Effects Tables, and MCDA methods) and provide a tool kit or suite of acceptable methods.

SECTION	ISSUE	PROPOSED CHANGE
Develop an Evaluation Plan to Ascertain the Impact of the Benefit-Risk Framework in the Human Drug Review Process		
Conduct Two Public Workshops on Benefit-Risk Considerations from the Regulator's Perspective		
FDA's Patient-Focused Drug Development Initiative		
Page 6	This section indicates that the FDA recognizes the importance of enabling meaningful patient input in helping to inform the context for drug development and regulatory decision-making, including FDA's B/R assessment.	BIO requests that the FDA also indicate that patient experience will be reflected in regulatory decision-making as it relates to product labeling as well as the B/R framework.
Page 7	The PFDD meetings were a great first step and provided a solid foundation for patient engagement; however, questions remain regarding how the FDA plans to utilize the patient input to inform regulatory decision making, including in the official assessment of the benefits and risks for individual treatments. Individual patient stories illuminate the day-to-day difficulties of living with a disease and offer insights into patient's perspectives about the benefits, risk tolerance, and tradeoffs of a potential treatment. However it is unclear how the FDA will use that data to inform regulatory decision making, including the B/R assessment.	BIO requests that the FDA provide clear guidelines regarding how the agency will synthesize and analyze patient experience data, how the review division will utilize this information at the reviewer level, and how this will be systematically implemented across the agency.
Other Activities		
Page 8	The FDA mentions the International Conference on Harmonization (ICH) opportunity to update its guidelines document M4E: The Common Technical Document (CTD).	BIO encourages the FDA to collaborate with ICH during the development of the draft guidance on B/R assessment for new drugs and biologics so as to support harmonization between international regulators (i.e., European Medicines Agency PROTECT).
IV. SUMMARY OF THIRD-PARTY EVALUATION CONDUCTED IN PDUFA V		

SECTION	ISSUE	PROPOSED CHANGE
Page 8	The contract evaluator noted variability in the lengths of completed B/R frameworks, types of content presented, and approaches to presenting content.	The observation by the contractor speaks to the need for additional training and guidance so that reviewers approach B/R assessments consistently. BIO requests that the FDA provide consistent information to Sponsors regarding how the information in the submission is weighted or valued, and what information is the most important for decision-making and why.
V. PDUFA VI COMMITMENTS ON ENHANCING BENEFIT-RISK ASSESSMENT		
Continue Implementation of the Benefit-Risk Framework		
Page 10	In this section the FDA indicates that during PDUFA V, FDA explored opportunities to apply the B/R framework to support internal discussions on complex postmarket B/R assessments. The section also indicated that in PDUFA VI, FDA plans to continue to explore more systematic use of the B/R framework in postmarket review but provides little detail regarding how that might occur.	BIO request that the FDA provide general information regarding leveraging learnings from PDUFA V and how FDA has or will apply a specific B/R framework in the post-market setting moving forward. BIO also asks that future evaluations also assess the quality of the content included in the B/R assessment which may include how the information included in the framework is valued and/or weighted. BIO also request that the FDA clarify whether the B/R assessment and framework will be considered a living entity that is updated each time new information is gathered in post-market setting, as opposed to a single point-in-time assessment of the basis for approval at the time of product approval.
Participate in Stakeholder Meeting on Benefit-Risk Assessment		
Draft Guidance on Benefit-Risk Assessment for New Drugs and Biologics		
Page 11	The FDA indicates that it is anticipated that this draft guidance document, when finalized, will provide drug sponsors and other stakeholders with a clearer understanding of how considerations on a drug's benefits versus risks factor into FDA's regulatory decisions throughout the drug development life-cycle,	BIO recommends that the FDA incorporate into guidance information regarding how it will use the B/R assessment grid to guide decision-making throughout the product lifecycle, not just at point of marketing authorization application. We also recommend the guidance provide specific details regarding when and how sponsors can

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	including premarket and postmarket phases but lacks information regarding whether the FDA will address FDA-Sponsor engagements around the B/R framework and additional analytic and descriptive tools to support the robustness of the B/R assessment.	engage with FDA to discuss aspects of the product's B/R assessment methodology and approach. We recommend the guidance also specify whether and to what extent which additional analytic and descriptive tools can be used by sponsors to support the robustness of the B/R assessment.
Conduct Second Evaluation of the Benefit-Risk Framework		
Page 12	BIO appreciates the information provided by the third party review, however there are additional points that could be addressed in the next review.	BIO requests that as a part of the second evaluation, the third party evaluator ask questions regarding how the structured B/R framework could be used throughout the product lifecycle, not just at a point of the marketing authorization approval. Additionally, a graphic indicating time points when such work should be done in a product's lifecycle would be highly beneficial for industry. Finally, BIO also asks that the second evaluation also examine how the FDA's B/R framework may better align with similar efforts outlined by the European Medicines Agency.
VI. ADDITIONAL OPPORTUNITIES TO ENHANCE FDA'S BENEFIT-RISK ASSESSMENT		
Improving accessibility of Benefit-Risk Frameworks for Approved Products		
Use of Benefit-Risk Frameworks to Support Advisory Committee Meetings		
Exploring Additional Tools to Support Benefit-Risk Assessment		
VII. CONCLUSION		