Biotechnology Industry Organization

May 7, 2013

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

Re: Docket No. FDA–2013–N–0196: Food and Drug Administration Prescription Drug User Fee Act V Benefit-Risk Plan; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the FDA Draft Plan on "*Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making.*" BIO supports FDA's publication of the draft 5-year plan and stands ready to work with the Agency as the methodology is further refined and integrated into the drug and biologic review process.

BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO believes that the proposed framework represents an important advancement in drug and biologic regulation because it reflects and reinforces the underlying reality that the FDA drug review process must be grounded in a careful evaluation and balance of both benefits and risks. Further, benefits-risk determinations must also be made in the broader context of disease severity, patient perspectives, and the body of available scientific evidence. As FDA notes, all drugs have some ability to cause adverse effects. Therefore, it is essential for the public to understand that safety is not an absolute; rather, the acceptability of the safety of a drug is assessed in the context of whether its benefits outweigh its risks. BIO supports FDA's continuing efforts to enhance the clarity of this complex and critical process of benefit-risk assessment, both internally and for the public, throughout the lifecycle of drug evaluation.

We are pleased to offer the following general and specific comments in support of the 5-year plan.

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GENERAL COMMENTS

I. Application of the Framework during Drug Development

To foster an environment in which all stakeholders can better understand FDA's thinking around a drug or biologic's benefits and risks, we request that FDA expand upon this framework in a guidance document to ensure that the framework can serve as a useful resource to both FDA and other parties, such as advisory committee members and industry Sponsors.

BIO believes that the framework holds promise for developing a common FDA-industry understanding during the drug development phase of how benefit-risk will be assessed in a particular disease area. For instance, the framework could be utilized as a helpful FDA-Sponsor communications tool as early as the end-of-phase II meeting. Further, the framework could be used as a tool in the same way that the Target Product Profile is used, and would not be considered a binding document, but could serve as a platform for discussion at appropriate meetings. Thus, the framework would serve as a commonly accepted decision-support tool for industry utilization, for example to help inform a Sponsor's decision to advance or discontinue a clinical development program.

However, use of the framework earlier in drug development is not discussed in the proposed plan. We welcome FDA guidance to outline a pathway over the next several years for refining, evaluating, and implementing the framework earlier in the drug development process.

II. Use as a Communication Tool during the FDA Review Process

We also agree that the use of the framework as part of Advisory Committee background packages may quickly orient the committee to the important review issues in the application under discussion. We believe that with additional enhancement, this tool will be useful in guiding the discussions and increasing transparency and consistency of recommendations at Advisory Committee meetings, by ensuring that the FDA Advisors focus on the issue of benefits and risks based on a structured framework.

Additionally, as FDA develops the Benefit-Risk framework for use in the approval action package and discussions with the Advisory Committee, we encourage FDA to share the document with Sponsors as part of the Late-Cycle Meeting in the NME Review Program so that the Sponsor may better understand FDA benefit-risk perspectives and prepare for the Advisory Committee meeting. This may enable timely resolution of Agency concerns that would otherwise lead to a second review cycle, delayed approval, and delayed patient access to new therapies.

III. Utilization of the Framework in the Post-Market Setting

We believe it is appropriate to apply this framework in both the pre-market and post-market contexts, as the regulatory decisions in both settings must carefully balance benefits and risks. We look forward to more information about the processes that will be used to update product-specific frameworks as new information is received in the post-market period and encourage FDA to use a transparent, systematic process to

incorporate post-marketing data into the framework. For example, what is the threshold or criterion for which "new information" will trigger the review of a product's risk-benefit profile? Who will be responsible for updating an existing product framework and what will trigger that process? As FDA notes, the basis for findings on the post-market setting comes from sources of varying levels of rigor. It will be essential that FDA employ a systematic approach to updating product-specific frameworks in the light of new evidence, and for communicating updated frameworks to Sponsors and the public.

IV. Risk Management Considerations

We also note that the framework calls for inclusion of the risk management (RM) strategy as a key element and for a summary of the "evidence and uncertainties" associated with the proposed RM strategy. We would appreciate the inclusion of examples demonstrating how "evidence and uncertainties" associated with the proposed RM strategies are to be included in the framework.

In the context of a post-market revision to a product's benefit-risk framework, BIO requests clarification on what types of evidence would demonstrate the RM strategy's success in the market. We would welcome empirical examples to demonstrate how the strategy's effectiveness is to be assessed in the market and incorporated into the framework.

V. Qualitative and Quantitative Methodologies

BIO also appreciates FDA's articulation of a *qualitative* benefit-risk framework that can serve as a communication and decision support tool. More transparent, structured articulation of FDA's reasoning related to benefit-risk assessment will help FDA enhance consistency in the review process, and allow Sponsors, physicians, and patients to understand the process that informed the drug review team's benefit-risk determination.

It is important to discuss how this qualitative methodology and *quantitative* data can be mutually complementary. For example, the plan reads "FDA considers it most important to be clear about what was considered in the decision, to be as quantitative as possible in characterizing that information, and to fully describe how that information was weighed in arriving at a conclusion." (p.4)

We believe that the framework should include both quantitative and qualitative methods as part of a toolbox to enhance regulatory decision-making, including a more comprehensive explanation of the appropriate use of quantitative methods and a description of the use of non-quantitative methods, such as categorization and ranking, to weight factors. It is important for FDA to clarify the role played by quantitative methods as it would be imprudent to say that all quantitative approaches to benefit-risk assessment are inappropriate.

We would also welcome FDA efforts to further clarify that including quantitative methods in the benefit-risk framework does not mean that benefits and risks should be weighted and summarized down to one number. FDA's statements related to "quantitative decision modeling" overstate the case. While it is certainly true that decision analysis

models can be used to obscure rather than clarify a decision, and there is no common standard for their use in benefit-risk evaluation, we encourage FDA to acknowledge that in some situations the use of such models could be informative. "Quantitative" could be viewed as a guiding principle in comparing benefits against risks. We encourage FDA to explain that selective use of quantitative approaches would not make a benefit-risk decision for the reviewer, but may help a reviewer to logically examine how various components may contribute to a decision. In addition, such approaches would enable other stakeholders to clearly see the level of importance each factor was given in the decision-making process in a quantitative manner.

VI. Efficient Integration into FDA Workflow and Standard Operating Procedures

It is important that the framework be fully integrated into the review process in a manner that does not add additional burdens to reviews or contribute to delays in the approval process.

We believe that further development of the framework as a tool to assist reviewers will also enhance the ability of FDA and Sponsors to utilize the framework throughout the drug development process. Specifically, we ask FDA to consider the following recommendations:

- Question-Based Prompts: Please include in the framework and describe in the plan the question-based prompts that FDA has developed to guide framework completion. Examples of such question-based prompts were included in a recent FDA presentation and have also been considered by other international regulatory authorities.[1, 2]

- Summary of Key Value Judgments: Please include guidelines in the framework that direct reviewers to clearly separate data from their value judgments, so that clinical judgments will be explicit, transparent, and interpretable. For example, rather than just simple qualitative statements, we encourage the inclusion of a short factual summary of key data, and the development and use of more sophisticated methods to capture the reviewer's perspective and conclusion on the clinical meaningfulness of a given treatment effect, or on (un)acceptable risk (*i.e.,* in terms of incidence, severity, etc.), given the known benefit profile of a drug. When possible, it would also be helpful to have reviewers provide a description of how they balanced the benefits and risks and to describe the tipping point when risks or benefits outweigh the other, so that other parties have clear understanding of how the benefits and risks are assessed in the context of each other.

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[1] FDA, Patrick Frey, 2013 FDA-DIA Pharmacovigilance Meeting, January 15, 2013

[2] European Medicines Agency, EMA Guidance Document on the Content of the <Co->Rapporteur Day 80 Critical Assessment Report, 2013, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004800.pdf

- Examples of Completed Frameworks and Methods: Please include in the plan more examples of completed frameworks, especially demonstrating the framework's use in complex cases that do not rely on straightforward comparisons between benefit and risk. Additionally, please provide guidance regarding how benefits and risks will be evaluated in the context of clinical importance, particularly if those events reflect different clinical severities or long-term consequences. For example, an investigational cancer therapy may improve cancer-free and overall survival of the treated patients for 6 months to 1 year, but cause adverse events of nausea, rash, and infection. Using some type of quantitative framework would transparently compare the benefits and risks. We encourage the FDA to use such examples, and to consider incorporating tables or other graphical presentations of data, to clearly illustrate how reviewers compare benefits and risks. We welcome FDA's use of such examples to demonstrate when qualitative and/or quantitative methods would be preferred.

- Non-Clinical Disciplines: Furthermore, we would like to better understand how non-clinical decision-makers and their disciplines play a role in benefit-risk decision-making and how FDA plans to ensure that decisions come from the rich background of the multi-disciplinary team.

VII. One Framework Per Indication

We also request clarification that a different framework will be developed for each product indication, rather than a single framework for each product across all available indications. Each proposed product indication can present substantially different benefit-risk contexts and patient populations, which must be assessed individually.

VIII. Handling of Confidential Information

We would like to better understand the process for redaction of proprietary information and confidential commercial information, prior to posting of the benefit-risk assessment on the web. It is unclear whether the proposed frameworks will include trade secret or confidential commercial information that could undermine a Sponsor's competitive standing if publically disclosed, or whether that information would be redacted in a public version of the document.

IX. "Current Treatment Options" Should be Interpreted as the Medical Standard of Care, not a Comparative Effectiveness Standard

We request clarification that the scope of "current treatment options" includes both pharmacological and non-pharmacological care for the underlying disease. For example, a simple list of FDA-approved products would provide an incomplete picture of available care options for a given patient, such as surgical or medical interventions and palliative care. To help clarify that the proposed standard includes non-pharmacological options, we suggest that "current treatment options" be revised to "current standard of care."

We also note that while "current treatment options" may be part of FDA's overall considerations, FDA does not approve drugs based on a comparative effectiveness

standard. This important principle must be maintained; imposition of a *de facto* comparative effectiveness standard would make many worthy drug development programs infeasible.

X. Incorporating Patient Perspectives into the Framework

We request greater clarity in FDA's process for incorporating patient perspectives of benefit-risk, disease severity, and the current standard of care. For example, how will the Agency translate the outcomes and feedback from the patient-centric drug development meeting on twenty disease areas into the proposed benefit-risk framework for specific products to treat those diseases? How will patient views be collected from this program be populated into the chart? We encourage FDA to update the 5-year plan and framework to include the PDUFA V program for how FDA will incorporate perspectives from the disease area meetings into the Agency's decision-making.

XI. Global Evaluation of Benefit-Risk and Harmonization

We believe that the fundamental principles supporting FDA's proposed benefit-risk plan are similar to other global initiatives. We encourage FDA to continue engaging in dialogue with other regulatory agencies on methodologies of assessing benefit-risk that acknowledge and reflect the global endeavor of drug development and regulation in which Sponsors operate. This important discourse can serve to advance the goal of developing a globally harmonized framework for benefit-risk evaluation to support decision-making.

We also note that "benefit-risk assessment" in the draft plan appears to mean the same as "benefit-risk evaluation" in the ICH E2C (R2) guidance. We encourage FDA to clarify whether the "benefit-risk assessment" in the draft plan is equivalent to the "benefit-risk evaluation" in the ICH E2C(R2) guidance.

Additionally, we encourage FDA to promote harmonization in benefit-risk methodologies across FDA's medical product centers, especially as it relates to combination products. While we appreciate that the plan is specific to CDER and CBER under the PDUFA program, please consider reference to CDRH's work in benefit risk decision making for devices (*e.g.,* the CDRH guidance on benefit-risk factors, and other Centers' frameworks, if relevant). This allows the reader to understand that the drug regulatory decision framework may not be applicable to animal products or human device products. If there is any effort to coordinate or ensure Center's approaches are harmonized when applicable (or if not due to legal differences), it would be helpful to have a footnote about this, as to the public might assume that FDA medical products would have commonalities.

XII. Evaluation of the Framework

Finally, we look forward to seeing FDA's plan for evaluating the impact of the framework and urge the Agency to move forward expeditiously to articulate this plan.

CONCLUSION

BIO appreciates this opportunity to comment on the "FDA Draft Plan on "*Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making."* Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
INTRODUCTION		
Page 1:	The first paragraph describes the qualitative approach as a subjective one: "This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence." In the second paragraph, the document criticizes quantitative approaches as having a subjective element: "Others, however, are skeptical of fully quantitative approaches, and consider such attempts to be a highly subjective exercise…"	Please resolve conflicting statements and correct statements that imply that quantitative methodologies are more subjective or just as subjective as qualitative assessments.
BACKGROUND ON FDA'S FRAMEWORK FOR DRUG REGULATORY DECISION MAKING		
1. DRUG REGULATORY DECISION-MAKING – AT THE INTERSECTION OF LAW, SCIENCE, MEDICINE, POLICY, AND JUDGEMENT		
Page 1-2:	The text reads "Beyond the clinical study of drugs, the Agency must also consider how people will actually use newly approved drugs once they are marketed."	We believe that considerations of off-label use should not affect the approvability of a product. Please clarify how FDA would incorporate potential benefits and risks from off-label use into the assessment of a product, given the potential impact on benefits and risks from such off-label use is unknown at the time of review and approval.
Page 1-2:	We suggest the following concluding paragraph to tie together several common themes in the plan.	We suggest adding the following at the end of the section: "This is the reason that it is so imperative to develop and establish a structured framework, which will help to

SECTION	ISSUE	PROPOSED CHANGE
		delineate how the decision is made, and potentially reduce the subjective component in the decision-making process, and create a common model that is reasonable from clinical and scientific perspective and can be used for benefit-risk evaluation for all stake holders."
2. DEVELOPMENT OF A BENEFIT-RISK FRAMEWORK		
Pages 5-6: Section 2.2	*Analysis of Condition and Current Treatment Options* provide a summary and assessment of the severity of the condition that the product is intended to treat and other therapies available to treat the condition. This represents the context of the decision that can provide useful information for weighing the benefits and risks of the drug under review.	We suggest that FDA includes in the plan that these factors are disease-specific (versus drug-specific) and may be applicable to other products in the same class of drugs. Please further clarify how and why these factors have any significant impact on the benefit-risk evaluation (assuming there is a pre-agreement with FDA on the primary study endpoint(s) for pivotal studies), particularly given that those studies are not intended for indirect comparative effectiveness. We also suggest that "Current Treatment Options" be revised to "Current Standard of Care"
Page 6: Section 2.2	*Risk Management* provides a summary and assessment of any efforts that could help to mitigate the identified safety concerns, or ensure that the drug is directed to those patients for whom the risk is considered acceptable.	Please revise the text to read: "*Risk Management* provides a summary and assessment of any efforts that could help to eliminate, minimize or mitigate the identified safety concerns, or ensure that the drug is directed to those patients for whom the risk is considered acceptable." Additionally, while many components of a risk management plan cannot be characterized quantitatively, the impact of

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		some can be estimated or modeled. We suggest that the framework recommend that reviewers include, when possible, assessments of the how data for benefit and risk endpoints, characterized in earlier sections of the framework, would be altered by the risk management plan.
Page 6: Section 2.2	*Evidence and Uncertainties* presents the facts, uncertainties, and any assumptions made to address these uncertainties that contribute to the assessment of benefit and risk.	Please revise to emphasize the inclusion of a short factual summary of key data, in addition to the other listed items.
Page 7-8: Section 2.3	*Pilot Project (FY 2012)*	We encourage FDA to expand this section to incorporate examples of and commentary about the benefit-risk frameworks that were included in FDA reviews of applications in the pilot, to increase transparency and provide a more thorough understanding of the background information and thought processes that went into development of the framework. We note that certain reviews posted on the FDA website for NMEs approved in 2012-2013 include sections on "Risk Benefit Assessment" and are presumably for products in the pilot, but the reviews alone do not provide FDA's conclusions about the content of those sections.
BENEFIT-RISK FRAMEWORK IMPLEMENTATION IN PDUFA V		
3. FY 2013 – FURTHER DEVELOPMENT OF THE FRAMEWORK		
Page 8-9: Section 3.2	*Adaptation to Key Considerations in the Post-Market Setting*	We encourage FDA to use a transparent process to develop a systematic approach to incorporate postmarketing data into the framework. The FDA framework should address how the Agency anticipates using these periodic

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		reassessments and analyses to update the benefit-risk framework. For example, will FDA update the benefit-risk assessment that was posted at the time the product was approved? Will re-analyses be performed? What are the expectations and process for updating the benefit-risk framework when PBRERs are evaluated? We also request that FDA expand this section to further describe current thinking on how postmarketing studies will be included in the benefit-risk evaluation framework, given that the postmarking safety information could include spontaneous reports, database studies, observational studies, *etc.*, which all suffer from a different level of uncertainty about causality than is available in clinical trial data.
Page 9-10: Section 3.3	*Characterization of Uncertainties in Benefits and Risks* Benefits are usually relatively easy to define, based on the level of statistical and clinical evidence associated with them in clinical trials, and the consistency of their results across studies. On the other hand, it is usually more difficult to define the risks, especially those that occur rarely. Invariably, there is differing perspective between industry and FDA on what the risks are. The structured framework should define how benefits and risks will	The examples of "uncertainty" provided in the FDA draft plan (*i.e.*, absence of information, conflicting findings, marginal results) are helpful in understanding to what uncertainties the Agency is referring. However, we ask that the Agency include more information regarding how risks will be determined and how uncertainty will be handled in the benefit-risk assessment. This information should also specify links between the benefit-risk assessment, uncertainty, and labeling.

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	be determined (*i.e.*, what level of evidence will be used to determine that a risk exists), understanding that FDA does need some flexibility and judgment in this regard. The level of evidence used to determine a risk should also be linked to how/whether it appears in labeling. For example, FDA could define tiers for different levels of evidence; those with the highest level of evidence would be accounted for in the benefit-risk decision and in labeling and those with lower levels of evidence would not. The purpose of this document is to provide an implementation plan; criteria for defining which benefits and risks are considered in the benefit-risk assessment, particularly in relation to uncertainty, will be necessary for reviewers. Weighting issues should also be considered.	
5. TRAINING AND COMUNICATION		
Pages 10-11: Section 5	It is unclear if Sponsors have the opportunity to review the benefit-risk frameworks before they are posted. What is the plan for engaging the Sponsor throughout the review process on the development of the framework as it develops? When should the Sponsor first propose a benefit-risk framework pre-	Please provide additional detail on the public availability of the benefit-risk frameworks and the engagement with the Sponsor throughout its development.

SECTION	ISSUE	PROPOSED CHANGE
	approval (*e.g.*, end of phase 2)?	
7. BENEFIT-RISK ADVISORY GROUP		
Pages 11-12:	*Benefit-Risk Advisory Group*	We suggest that FDA include industry representatives on the Benefit-Risk Advisory Group. Industry experts who are familiar with both the theoretical approaches to benefit-risk as well as the practical issues to arise when designing, analyzing and reporting benefit-risk may provide critical input in designing a framework that succeeds in the first round of use and has far fewer rounds of revision.
ADDITIONAL PDUFA V COMMITMENTS ON ENHANCING BENEFIT-RISK ASSESSMENT		
10. PATIENT FOCUSED DRUG DEVELOPMENT		
Page 13:	It is unclear how patient-focused drug development work will tie into the structured benefit-risk assessment framework.	Please add clarification.