May 7, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to the Food and Drug Administration’s (FDA) request for comments on its Draft PDUFA V Implementation Plan: Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making dated February 2013. PhRMA is a voluntary, non-profit association that represents the country’s leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested approximately $50 billion in 2012 in discovering and developing new medicines, representing the vast majority of private investment in new medicines in the United States. PhRMA member companies are committed to the development of innovative, life-saving and life-altering treatments and cures for serious and life-threatening conditions. To that end, PhRMA applauds FDA’s effort in developing this implementation plan and for advancing progress against this important PDUFA V performance goal.

PhRMA is committed to helping ensure that patients have access to safe and effective new medicines. In pursuit of this goal, we strongly support the FDA in its efforts to implement a structured approach to benefit-risk assessment. PhRMA shares FDA’s belief that the value of a structured approach is to improve and facilitate communication between public stakeholders, including patients, consumers, healthcare professionals and sponsors, regarding the benefits and risks of existing and new medicines. Another benefit of a structured approach is to promote consistency in the assessment of what information and data are relevant and most impactful in consideration of benefit-risk balance. PhRMA believes that the Benefit-Risk Advisory Group’s role in reviewing completed benefit-risk frameworks can further support this objective. In addition, a repository or case record of benefit-risk decisions (along with their context and rationale) using a structured framework will be a useful reference for the Agency and should advance the FDA’s
efforts to achieve greater consistency in the regulatory review and decision-making process. Furthermore, PhRMA supports the FDA’s focus on a strategy for implementation of a structured approach to benefit-risk assessment that is minimally burdensome and as seamless as possible for the reviewers. Therefore, PhRMA agrees with the FDA that the best way to achieve this objective is to fully integrate use of the framework into FDA’s standard review processes at the appropriate times during regulatory review. PhRMA looks forward to FDA’s development of supporting implementation materials and updates to the Agency’s Manuals of Policies and Procedures (MaPPs) to ensure clear, consistent, and efficient implementation of a structured approach to benefit-risk assessment across its review divisions.

PhRMA fully appreciates that regulatory decision-making requires use of appropriate flexibility and reliance on expert judgment due to the complex nature of regulatory decisions and different perspectives on benefit-risk balance. Therefore, PhRMA supports FDA’s plans to implement a qualitative framework for benefit-risk assessment, recognizing that the use of quantitative tools, in certain circumstances, can be helpful in supporting greater clarity of the thinking behind an assessment, especially if the overall assessment is complex in nature. We encourage FDA to include in the plan an acknowledgment that quantitative tools can be appropriately employed to complement a generally qualitative approach to benefit-risk assessment.

With respect to the structure and elements of the FDA benefit-risk assessment framework, PhRMA believes that FDA is proposing a model consistent with the current best thinking on how to approach benefit-risk assessment in a systematic manner. In terms of the summary assessment, PhRMA agrees that the impact of the benefit-risk assessment on labeling, the requirement for REMS and the need for post-marketing requirements / post-marketing commitments is extremely important.

In the comments that follow, PhRMA would like to highlight areas for which we are supportive of continued work by the FDA and areas where greater clarity from the FDA would be helpful:

I. The benefit-risk framework should be used to facilitate and improve the quality of interactions between sponsors and FDA during the review process.

- PhRMA believes that the benefit-risk framework should become a key component of communication between FDA and the sponsor during the review process. PhRMA encourages the FDA to think about ways to use the benefit-risk framework to facilitate discussions with sponsors at the mid cycle and late cycle meetings. PhRMA believes that discussion between sponsors and FDA of interim assessments of benefit-risk balance at critical points during the review process will facilitate a more efficient and high quality review of a new medicine. Further, PhRMA believes there is value in the FDA’s sharing of the framework with the sponsor at the end of the review, particularly in the event of a complete response letter. Finally, PhRMA encourages the FDA to consider use of a structured approach to benefit-risk assessment as a means to facilitate discussion at Advisory Committee meetings.
- While PhRMA understands that one of the primary uses of a framework will be to facilitate internal decision-making within the Agency, PhRMA encourages the FDA to
consider what information sponsors can provide to support FDA’s assessment of benefit-risk, either in marketing applications, during review, or in post-marketing safety reports. PhRMA believes that it may be valuable for sponsors to provide their perspective on benefit-risk balance utilizing the principles of the FDA’s structured approach to benefit-risk assessment with their application to guide discussion with the Agency about potential differences in perspectives on benefit-risk balance among stakeholders.

- PhRMA would like to understand if sponsors will have the opportunity to review the FDA’s benefit-risk framework for their products before the assessment is posted.
- Lastly, PhRMA encourages FDA to consider the potential role of the benefit-risk framework earlier in drug development; for instance, there may be value in discussing the benefit-risk framework at end-of-phase 2 meetings, in order to ensure alignment on identified and potential risks and benefits, critical efficacy and safety assessments, and risk mitigation strategies in phase 3 clinical trials.

II. The consistent use of a standard framework across review divisions is extremely important. PhRMA is supportive of the Agency’s efforts to integrate the framework into the review process.

- We look forward to understanding the methodological details that will underpin the development of the framework, as outlined in the “question-based prompts to direct reviewers’ completion of the framework”. PhRMA welcomes any opportunity to provide feedback on the question-based prompts.
- PhRMA looks forward to the FDA’s update of MaPPs and review templates to include guidance for reviewers on the use of a structured framework for benefit-risk assessment. PhRMA believes that successful implementation of a qualitative framework will hinge on the FDA’s ability to ensure consistent use of the framework among reviewers in the same review division and also across review divisions, particularly how each reviewer reaches a conclusion about the benefit-risk balance based on their interpretation of the data and expert judgment of the relative importance of the benefits and risks of the medicine given the decision context (e.g., severity of the disease, unmet medical need). Furthermore, guidance for reviewers as to how uncertainties should be handled in the benefit-risk framework is also important.
- PhRMA supports FDA’s efforts to advance patient-focused drug development, and we applaud the Agency for the recent announcement and start of public meetings for specific disease areas. PhRMA looks forward to the FDA’s proposal for how the Agency will incorporate patient perspectives into regulatory decision-making, particularly the process for integrating any differences in perspective (e.g., regulator, patient, caregiver) into the final benefit-risk assessment.¹
- PhRMA understands that post-marketing commitments are designed to further investigate areas of uncertainty at the time of marketing approval and that REMS programs would be implemented when there are manageable risks that will shift the benefit–risk profile for the indicated population. Clarification on how the Agency will

integrate the potential mitigating benefits of a proposed REMS into the benefit-risk assessment framework would be helpful.

III. PhRMA understands that the benefit-risk assessment will evolve in the post-marketing setting when Periodic Benefit-Risk Evaluation Reports (PBRERs) are submitted. It would be useful to further understand this process, including the frequency of updates, what types of new information would trigger an update to the framework, and how the quality of the post-market data will be factored into an updated assessment.

IV. While PhRMA believes that the principles of FDA’s approach to benefit-risk are generally aligned with other global initiatives, we encourage FDA’s continued dialogue with other regulatory agencies on methodologies of assessing benefit-risk to advance global convergence of approaches that are necessary for global development of new medicines.

In conclusion, PhRMA strongly supports FDA’s implementation of the proposed structured benefit-risk assessment framework, and PhRMA stands ready to assist FDA with this implementation. A key to its success will be the acceptability of the framework to FDA reviewers. PhRMA believes that embedding the framework into existing FDA regulatory decision-making processes as a means to make reviewer judgment explicit in regulatory decisions is crucial to minimizing burden on reviewers and fostering acceptance, use, and consistency across the Agency. PhRMA views the most important potential benefits of the framework to be: 1) increased transparency and communication of regulatory decision making processes between FDA and Sponsors during drug development and review; 2) increased consistency in regulatory decision making across reviewers through common definitions, processes, and methods; 3) increased opportunity to facilitate internal alignment and decision making at FDA; and 4) systematic consideration of the patient perspective into the regulatory decision making process. PhRMA looks forward to continuing to work with FDA and other stakeholders on this implementation. PhRMA further hopes that these comments provide a foundation for important topics to be discussed in the upcoming public workshops and would welcome opportunities to work with the FDA to ensure the success of these important PDUFA V workshops.

If you have any questions, please do not hesitate to contact PhRMA.

Respectfully submitted,

[Signature]

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