Biotechnology Industry Organization

July 25th, 2013

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

Re: Docket No. FDA–2013–N–050: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies; Notice of Public Meeting; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the issues and challenges associated with the standardization and assessment of risk evaluation and mitigation strategies (REMS) for drug and biological products. BIO supports FDA's ongoing PDUFA V initiatives to identify potential projects that may help standardize REMS and integrate them into the health care delivery system.

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 has long advocated for a holistic approach to drug safety, and the PDUFA V framework demonstrates industry's commitment to a lifecycle approach to product evaluation by strengthening FDA's post-market surveillance and benefit-risk management capacity. Drug safety is not absolute, but rather a matter of balancing a drug or biologic's predicted benefits against known risks. A product is considered safe if it has an appropriate benefit-risk balance for the intended population and use, and a REMS program can play an important role in minimizing risk to maximize the drug's potential benefit-risk profile. Effective risk management approaches, including REMS, can help facilitate appropriate patient access to efficacious therapies with known safety issues that may not otherwise receive FDA approval.

As the Agency continues its efforts to make REMS less burdensome to all stakeholders, and more predictable and simpler to understand, implement, and measure, BIO asks the Agency to keep in mind the following principles:

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1. FDA and Sponsors should communicate about REMS and risk management strategies as early as possible in the review cycle;

2. Comprehensive REMS implementation efforts should be reserved for REMS with elements to assure safe use (ETASU) programs;

3. Standardization should include establishing a standard set of best practice principles regarding the design, development, testing, implementation, evaluation, modification and termination of REMS tools; and

4. REMS program effectiveness assessments should evaluate the totality of the REMS program.

1. REMS Communication: Early and Often

To better standardize REMS program, it is critical that FDA and Sponsors initiate risk management planning and dialogue early and often during product development and the FDA review phase. FDA and Sponsors require an understanding of when and how to communicate regarding potential REMS. For this reason, the PDUFA V NME Review Program provides structured opportunities for FDA-Sponsor communication at key points in the review, including the pre-NDA/BLA meeting, mid-cycle communication, and late-cycle meeting. The Program also promotes early cross-disciplinary engagement by staff of FDA's Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE) to assess if a REMS is needed to mitigate a potential safety issue. By proactively discussing risk management strategies and potential REMS earlier, FDA and Sponsors can reserve adequate time in the review process to develop an optimized and standardized REMS program that can minimize the burden on the healthcare delivery system.

BIO is looking forward to the release of the independent contractor evaluation of the NME Review Program in 2015 so that we can better assess if risk management discussions are in fact taking place earlier than previous experience. We also look forward to evaluating how early communication and draft REMS proposals align with application requirements ensuring that all commitments for a "complete submission" made at pre-submission have been addressed.

2. REMS resources should be reserved for programs with elements to assure safe use (ETASU)

Secondly, to ensure that approved REMS can be efficiently and effectively implemented, BIO believes that REMS efforts should be reserved primarily for REMS programs that include Elements to Ensure Safe Use, or ETASU.

Many approved REMS consist of only communication-based risk management strategies, rather than the more restrictive ETASU tools. For example, as of July 2013, only 36 of 72 approved REMS included ETASU, while the remaining fifty percent of REMS focused solely on patient and provider communication elements through MedGuides and Communication Plans.[1]

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[1] FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)*, accessed July 24, 2013,

BIO believes that patients and physicians need timely, accurate, and relevant information about the benefits and risks of a drug or biologic so that they can make well-informed choices about therapies, but we think that that more meaningful progress in effectively communicating benefit/risk can be achieved through complementary mechanisms outside of REMS programs.

For example, BIO supports FDA's ongoing initiative to develop Patient Medication Information (PMI), a single, unified patient benefit/risk communication tool that would minimize redundancies and public confusion around the distribution of MedGuides, patient package inserts, and Consumer Medication Information (CMI). Additionally, FDA's November 2011 guidance clarifying that MedGuides can be administered outside of the context of a REMS was an important step in improving the efficiency of the REMS framework. We encourage FDA and stakeholders to also evaluate whether effective and efficient benefit/risk communication is better achieved by limiting communication plans to ETASU REMS to explain restricted distribution plans to patients and providers, and by implementing routine benefit/risk communication for all non-ETASU drugs outside of the context of the REMS program.

These various approaches have the dual benefit of enhancing benefit/risk communication towards patients and providers while reserving comprehensive REMS implementation efforts for ETASU programs, so that all stakeholders in the healthcare delivery system can focus limited attention and resources on the most critical risk minimization activities. With this in mind, we suggest that priority projects for standardizing risk management tools under the REMS Integration Initiative should focus primarily on ETASU REMS elements.

3. Standardization should include establishing a standard set of best practice principles regarding the design, development, testing, implementation, evaluation, modification & termination of REMS tools

BIO supports FDA's efforts to standardize REMS, where appropriate, with the goal of reducing the burden of implementing REMS on practitioners, patients, and other various health care settings. While REMS standardization can help eliminate unnecessary variation between REMS programs, it should be noted that standardization for the sake of standardization alone is not always consistent with best practices in managing the diverse risks associated with different types of products.

BIO recommends developing a standard set of best practice principles regarding the design, development, testing, implementation, evaluation, modification and termination of REMS tools, which will promote program stability while at the same time preserving the necessary flexibility to address and mitigate product specific risks and associated REMS goals. These principles should include a shared understanding between FDA and Sponsors of the standard principles and methods used by FDA to assess and characterize risks and related appropriate REMS tools or interventions. BIO looks forward to working the FDA to develop these best practices to ensure they are based on practical evidence and the latest advancements in the science of pharmaceutical risk management.

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http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

4. REMS Program Effectiveness Assessments

Finally, BIO supports the development of an evidence-based approach to measuring the effectiveness of REMS. BIO believes any successful program assessment requires FDA and Sponsor understanding and prior agreement on outcome goals. Without such shared understanding and agreement, assessment tools may not properly measure and capture whether any given program is appropriately mitigating identified risks necessary to ensure that a drug product's benefits outweigh those particular risks.

BIO also believes it is important that any assessment evaluate the totality of a REMS program. For example, while the availability of information about a drug can empower a patient to make sound decisions about his or her own health, it should be understood that patient knowledge of a specific risk does not always translate into actual behavioral changes that can in fact minimize the risk involved. This fundamental limitation should be acknowledged when assessing REMS tools and medical outcomes, especially in light of reliance on assessment surveys that measure understanding as opposed to behavior. A holistic approach to assessment should therefore also include measures of implementation fidelity, such as engagement with and adherence to program specific processes and procedures put in place to control exposure to risks and ensure proper use.

It is also important to recognize that program assessment tools can themselves can place a burden on the healthcare delivery system, including patient, prescriber and dispenser time and resources. As FDA's reliance on REMS grows, the effectiveness of the program and its burden on the overall healthcare delivery system must be carefully measured. Effective system burden measurement requires the collection and review of standard data that also look cross programs, products, and tools. As Sponsors are but one part of the healthcare delivery system and have limited access to such data, FDA and other REMS stakeholders should collaborate in collecting and evaluating system burden related data to judge whether particular REMS programs or tools overburden the health care system and modify REMS requirements accordingly.

CONCLUSION:

BIO appreciates this opportunity to comment on REMS Standardization. We look forward to continuing to work with FDA and other engaged stakeholders to further streamline REMS programs and minimize the burden on the healthcare delivery system.

Sincerely,

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