Biotechnology Industry Organization

September 16th, 2013

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

Re: Docket No. FDA-2013-N-0502: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments in response to its 2-day public meeting "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies."

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.

GENERAL COMMENTS:

As mentioned in our testimony at the public meeting (see Appendix A), BIO supports FDA's ongoing PDUFA V initiatives to identify potential projects that may help standardize Evaluating Risk Evaluation and Mitigation Strategies (REMS) and integrate them into the health care delivery system. 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.

BIO's testimony highlighted four main principles:

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

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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.

Below BIO provides responses and suggests projects relating to FDA's questions posed in the Federal Register Notice and the above stated BIO principles.

A. Prescriber-Directed REMS Tools

"REMS programs use a number of tools to educate prescribers and/or ensure that they carry out REMS requirements, including screening, monitoring, and counseling patients. These tools have included risk communications to prescribers, prescriber training, and instruments to help prescribers prescribe the drug safely—for example, counseling guides and checklists."

- **Continued Medical Education:** As a prescriber training tool, BIO supports the concept of incorporating REMS training into continued medical education (CME) platforms, including permitting REMS/CME training programs to be funded with unrestricted educational grants to third party CME providers. Such CME programs could also incorporate real time knowledge assessments allowing for continued training improvements to ensure prescriber understanding and comprehension.

  We believe the CME approach may offset the burden on prescribers with the CME credit earned, while at the same time communicating key product safety information. Before fully incorporating CME into REMS, BIO encourages FDA to fully assess the extended release/long acting opioid REMS CME program and to pilot additional programs to better understand associated prescriber REMS/CME training burdens and to develop best practices.

  The numbers of times that prescribers should be required to take REMS training (or re-enrollment) should be based on whether there are changes to the risks identified for the product and/or whether significant revisions are made to the interventions described as part of the REMS. We understand the preferred format is electronic media modules.

- **Standardized REMS Enrollment Form Template:** The Agency should also consider providing Sponsors with a prescriber enrollment form template. An enrollment form template may streamline the overall prescriber enrollment process and facilitate greater prescriber participation in REMS programs. As the enrollment form serves to confirm and affirm completion of REMS certification programs, we suggest that if a standardized template include risk and use

information, such information should not be required to be overly lengthy. The Agency should also consider providing an online enrollment platform, with all REMS available on one site for easier access and completion.

B. Patient-Directed REMS Tools

"REMS programs may use a number of tools to educate and counsel patients, provide patients with information about the risks of the drug, and help to ensure that patients use the drug safely. These tools may include patient enrollment in the REMS, patient monitoring, counseling by health care professionals, Medication Guides, and other patient-directed educational materials."

- **Patient Enrollment or Acknowledgment Forms:** Patient-directed REMS tools (such as enrollment or acknowledgment forms) should include information about both the potential benefits and risks of the product. However, when discussing risks, the patient-directed REMS tools should focus on the risks identified as the reasons for the REMS, rather than including detailed information about all risks associated with the product, which may dilute the message, and divert the patient's focus.

- **Single Web Portal for Patient REMS Information:** We also encourage FDA to leverage existing information technologies and to explore the use of the latest electronic technology (*e.g.*, quick response codes) to provide patients with immediate access to information, including the creation of a single Web portal that includes a patient specific gateway allowing access to the latest tools and materials and serving as a central information and reference source.

- **Pharmacist Engagement and Medication Therapy Management:** BIO also recommends the Agency explore methods to increase the involvement of pharmacists in communicating safety information to patients. We also recommend that FDA consider partnering with groups such as pharmacy organizations (*i.e.*, American Society of Health System Pharmacists (ASHP), American College of Clinical Pharmacy (ACCP)) and the Health Resources and Services Administration (HRSA) to identify practices for integrating REMS into medication therapy management, including evaluating when REMS have been fully integrated and thus may no longer be independently necessary.

- **Prescriber Surveys:** FDA should also explore the use of prescriber surveys to determine REMS burden and/or effect on patient access in settings where different treatment options are available, not all with REMS, and a prescriber considered a drug with a REMS but opted not to prescribe it because of the REMS related burden. In addition to interviews with prescribers, other methodologies, such as observational time-motion studies, or computer-simulated modeling exercises, should be considered as ways to gather data on REMS related burden. As Sponsors are but one part of the healthcare delivery system and have limited access to data, FDA and other stakeholders should collaborate in collecting and evaluating such information, especially because only FDA has the ability to collect and evaluate data cross programs, products, and tools.

C. REMS Tools in Drug Dispensing Settings

"Drug dispensing settings, such as prescribers' offices, hospitals, pharmacies (e.g., specialty, retail, and mail-order), integrated health care delivery systems, and infusion centers, often play a significant role in REMS. This is a challenging area to address because of the wide range of health care settings involved and because dispensers are frequently called upon to coordinate care across a range of health care settings and practitioners and to reinforce the tools that have been used by other health care practitioners. Specific dispensing settings may be required to obtain certification under a REMS, and, like prescribers, the health care practitioners who dispense a drug (authorized dispensers) may be required to complete training, counsel patients, and provide patients with educational materials, including Medication Guides. In addition, dispensers may be required to document that certain safe-use conditions are met before dispensing (e.g., by ordering/checking lab tests or completing a form or checklist).

Many REMS with elements to assure safe use require that specific health care settings be certified to be able to dispense the drug. To certify the health care setting, REMS typically require a representative of that health care setting to agree that the health care setting will meet all REMS requirements, including the completion of any necessary training."

- **REMS Training for Multiple Dispensing Sites:** In healthcare settings with multiple dispensing sites where a single certification is required, the REMS program would need to ensure that training has been disseminated to individual practitioners at all sites covered under the single certification.

D. Approaches to Standardizing REMS Tools

"Many stakeholders have asked FDA to standardize specific REMS tools like stakeholder enrollments, Web sites, and educational materials. Standardizing REMS tools will require ongoing collaboration among FDA, drug manufacturers, stakeholders, scientific experts, and others. To ensure that standardized tools are effective and minimally burdensome, they should be developed in an open and inclusive process that incorporates the feedback of all relevant stakeholders as well as the latest science and best practices from across the health care system. To ensure the continued success of these tools, they must be updated regularly as best practices evolve."

- **Best Practices for REMS Design and Implementation**: 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 preserve 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 with 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.

- **Easily Identifiable Format for REMS Materials:** We also recommend that FDA develop a standard, easily identifiable format for REMS materials so that health care providers will immediately know that the materials are FDA approved REMS materials rather than promotional materials, to attempt to increase the likelihood that the REMS materials are opened and read rather than discarded. These materials should incorporate best practices in educational materials' design and be tested prior to broad distribution. We also encourage FDA to consider and pilot the use of alternative media forms to convey information and educate prescribers, such as interactive mobile device applications.

- **Data Standards for Class REMS Registries:** We also encourage FDA to initiate or align data standards for class REMS that require registry data collections. For example, in cases where REMS require registries to collect toxicity or other adverse events outcomes by class, data would be collected in a consistent manner from all Sponsors, so that new Sponsors could be added to such registries as new products in the class require the same registry data collections.

- **Single Web Portal for Standardized REMS Tools and Materials:** BIO also supports establishing an a single Web portal that acts as a repository for standardized REMS tools and materials and serves as a central information or reference source for REMS stakeholders. In order to ensure stakeholder confidence, FDA should back or sponsor the portal. To be truly effective and useful, such a portal should also provide separate access points for prescribers and patients.

E. Approaches To Assessing the Impact of REMS

Drug manufacturers are required to submit assessments of their REMS on a regular basis. To date, these assessments have tried to evaluate the effectiveness of the REMS by measuring the frequency of adverse outcomes of interest, the knowledge of stakeholders, and the compliance of stakeholders with certain REMS requirements. To accomplish this, drug manufacturers have relied on spontaneous adverse event reporting, knowledge surveys, and systems that track stakeholder completion of certain activities, such as enrollment and documentation of safe use conditions. To improve how REMS are assessed, FDA is considering additional areas for measurement and additional methods to measure the impact of REMS.

- **Prior Agreement on REMS Outcomes Goals:** 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.

- **Assessment of the Totality of a REMS Program**: BIO 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 behavior as well as knowledge and attitudes, and implementation fidelity (*i.e.,* the extent to which all program elements were executed as planned in the time specified).

- **Assessment of REMS Burden on the Healthcare System:** Effective system burden measurement requires the collection and review of standard data that also look cross programs, products, and tools. Sponsors do not have access to the required data to adequately assess the impact of REMS burden to the healthcare system. Sponsors should not be required to assess this burden as part of a REMS, rather FDA and 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 in response to its 2-day public meeting "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies." 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)

APPENDIX A

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:

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]

[1] FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)*, accessed July 24, 2013, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

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.

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,

/S/

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