Biotechnology Industry Organization

July 7, 2012

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

Re: Docket No. FDA–2012-N-0408: Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge; Public Workshop; Issue Paper

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on "Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge." BIO also appreciates that FDA is actively seeking stakeholder input on the issue, including by holding a June 7, 2012 Workshop on the topic and making available an Issue Paper that focuses on the use of surveys to assess patient and provider knowledge.

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:

BIO supports the Agency's efforts to develop guidance for industry describing best practices for conducting an assessment of a REMS goal regarding patient and/or health care provider knowledge about a drug's risk(s). In addition, BIO supports FDA's overall efforts to improve knowledge through the development and distribution of Patient Medication Information (PMI) that reinforces communication between the patient and healthcare providers, enhances understanding of benefits and risks of a product, and promotes safe and effective use of medication.

BIO agrees that assessment surveys are only one possible method that can be used to assess the extent to which patients/caregivers or health care providers understand the risks associated with a drug and/or how to use a drug safely. 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. These fundamental limitations should be acknowledged when assessing REMS tools and medical outcomes. Therefore, it is important to evaluate the totality of a

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REMS program. This can include engagement with and adherence to program specific processes and procedures put in place to control exposure to risks and ensure proper use.

BIO also shares the Agency's goal of reducing the burden of REMS programs on the healthcare delivery system by streamlining REMS tools and programs. REMS assessment survey tools themselves can place a burden on patient and prescriber time and resources, especially if the survey is very long or overly complicated. Assessment surveys to evaluate compliance with a REMS goal of informing/educating patients and/or health care providers should be used judiciously and in as efficient a manner as possible. BIO also encourages FDA to consider issuing guidance for when knowledge surveys are no longer needed, such as when REMS access related processes and procedures are extensive and outcome goals are being met.

COMMENTS TO SPECIFIC QUESTIONS:

1) What strategies can the applicant use to recruit a sample that is representative of the population that is prescribing / dispensing / taking the drug?

Recruitment strategies can include the engagement of pharmacy chains, physician offices, market research panels, existing registries, advertisements, and other available resources. However, while BIO understands the statistical importance of achieving a representative sample, the existence of many hurdles in achieving a fully representative sample necessitates flexibility, rather than rigid sample requirements.

For example, recruiting a representative sample first requires a determination of the population that is prescribing, dispensing or taking the drug. There may be a time lag associated with the initial deployment of the REMS program and the collection of this type of utilization data may not be available until the product has been on the market for months or years, and may also be dependent upon reimbursement and claims processing systems.

In addition, even after the correct population is identified, securing adequate participation is also an obstacle. Even with incentives, patients and providers may be unlikely to participate because of the burden on their time and resources.

a) Given that the applicant cannot compel an individual to complete a survey, is it acceptable to enroll a relatively small (making the survey feasible) number of participants that are representative of the totality of the health care provider or patient population and make generalizations from that sample to the larger population?

Yes, as long as the sample is reasonably representative and sized to give a meaningful result. Sample size should also be permitted to vary depending on the rarity and seriousness of the illness being treated. A patient survey related to a drug subject to a REMS for a rare, serious or life-threatening disease will be

inherently smaller (sample size and response rate) than that for a REMS of a drug used to treat a larger, healthier patient population.

b) What is an adequate sample size to be able to confidently extrapolate findings to the entire population prescribing/dispensing/taking drug?

The determination of an adequate sample size should be made on a case specific basis. As discussed above the rarity and seriousness of an illness will have an effect on confidence levels related to sample size and extrapolation to the larger population. When needed, sample size estimation may be based on standard and well published methods for sample size calculations.

2) Is the *knowledge rate* (i.e., the proportion of subjects who demonstrate knowledge of the risk message) the appropriate primary endpoint for a survey?

The primary endpoint for a survey is dependent upon the research question or objectives. If the research objective is to assess knowledge, then using a knowledge rate is an acceptable endpoint.

However, it is also important to distinguish between knowledge and memory. Although the FDA does not expect the prescribers and patients surveyed to recall the full prescribing information, this seems too often to be the case based on the length of surveys and amount of detail in the survey questions. (See question #7.)

a) What factors need to be considered when establishing the threshold for success for educational elements of the REMS?

Factors to consider when establishing a successful threshold include the following: the disease entity (*i.e.*, is the disease serious or life threatening; does it affect patient mental capacity, attention, communication, etc.), the REMS goals, research objectives, complexity of key risk messages, and characteristics of the population of interest (*e.g.*, comprehension level or mental state of the population). The Agency should also take into consideration whether or not there are other elements of the REMS that control risk beyond knowledge, such as blood tests that control access. If the REMS has multiple redundant systems and processes then the threshold for success may not need to be as rigorous.

b) Should the threshold for successfully meeting a REMS educational goal be set at a knowledge rate of 80 percent or 90 percent, or should it vary depending on the risk message? If it should vary, what should the minimum threshold for success be? Should the threshold reflect whether the product is a new molecular entity (NME) or original biologic product, or an older drug?

The threshold for successfully meeting a REMS educational goal should vary depending on the risk message. If the risk message is simple, clearly

identifiable, and easily understand by a broad population, then a threshold of 80% may be reasonable and obtainable. However, if the risk message(s) is complex, requires the patient to understand signs/symptoms, and/or is relevant only to a subpopulation of patients, then a threshold of 80% may not be reasonable or obtainable.

3) Since most surveys use only True/False and multiple-choice questions, what are the advantages and disadvantages of using other question types (open-ended, case vignettes, fill-in-blank) to evaluate knowledge?

In general, a survey should be simple, easy to answer, and easy to reproduce. Attention should be paid to overall length of the surveys to minimize the time and resource burden on both prescriber and patients. Lengthy and complex surveys can be associated with lower response rates.

While open-ended questions may be an effective way to measure higher cognitive objectives, they are difficult to judge objectively and can skew survey reliability. And while fill-in-blank questions can assess a wide range of content and minimize guessing compared to multiple-choice and True/False, rarely can they be written to measure more than simple recall of information and they also are plagued by the same problems of objectivity and reliability.

4) Please discuss process issues related to these surveys:

a) Given issues of recall, should the lag time between the REMS communication and the survey administration be standardized?

Guidance and standards should be provided for the lag time between the REMS communication and the administration of the survey. There are circumstances where lag times of 30, 60, or 90 days may be appropriate depending on the disease, the drug, and its administration.

b) Should pretesting/validation be required to reduce the likelihood of a poorly worded question that was not recognized during survey development?

Ideally, pre-testing on a small number of participants would be performed to assess the general understanding and readability of survey questions. However, in order to maintain flexibility, reduce burden, and prevent approval delays pre-testing should not be required.

c) On average, how long does it take to design, test, recruit participants, conduct, analyze, and report the results of a survey?

On average, it can take anywhere from 12 to 16 months to design, test, recruit participants, conduct, analyze, and report the results of a survey. Additional time, of 90 days or more, may also need to be factored in for FDA prior approval and negotiation and resubmission if needed.

d) Please comment on appropriate incentives for patients and health care providers to complete surveys.

Incentives are important for increasing survey participation. More often than not people will not participate in a survey, unless some form of incentive is provided. Moreover, the chance of bias may increase when an incentive is not provided.

In general, an incentive should be commensurate with the time and resources required to complete the survey. Cash incentives should be permissible. Incentives can also be made optional by allowing participants to either decline, accept, or donate the incentive to a relevant cause. Providing continuing medical education (CME) credits and research briefs may be effective at increasing response rates for prescribers; prescribers may even prefer receiving CME credits for their time. Also, an incentive that is viewed as a "token of appreciation," such as a nominal monetary incentive, may also increase prescriber participation.

5) Given the issues with surveys that we have observed, what are the alternatives to knowledge surveys to assess the effectiveness of the educational elements of the REMS? If any, what are the advantages and disadvantages of the alternatives?

Any alternatives to knowledge surveys should minimize the burden of participation on the population being assessed, being patients or prescribers. Moreover, formal assessments of knowledge outcomes should not be a prerequisite for analyzing the success of a REMS program, as the focus should remain on assessing the overall public health outcome.

For patients, perhaps more can be done using internet applications in the physician's office, at the pharmacy, or at home within 24 hours of picking up a prescription. There also may be a role for medical specialty organizations or medical professional societies in this process, particularly if their members are prescribing multiple products with REMS from many different sponsors.

6) What are the considerations in designing questions to assess the impact of REMS on patient and/or provider behavior and access to drug, as well as the potential burden of the REMS on these groups? What are alternative methods to assess behavior, burden, and access for REMS? If any, what are the advantages and disadvantages of the alternatives?

BIO supports REMS assessment processes and practices that are efficient, effective, and the least burdensome for patients, providers, and the health care system. The overall public health outcomes of the REMS should be the over-riding factor in determining the success of the REMS. Some possible strategies for consideration may include: conducting a database study using electronic health records or existing registries; watching, observing, and/or interviewing patients; and conducting focus groups.

7) Question for industry: From your perspective, what challenges have you encountered in designing and conducting knowledge surveys?

Knowledge surveys can be too detailed and lengthy if the REMS focuses on many risks and can require a prescriber to recall many of the details in the prescribing information – this can lead to confusion, impatience, and incorrect survey results. Follow-up surveys then face the same problem since the survey should stay the same to remain unbiased and provide a comparator.

CONCLUSION:

BIO appreciates this opportunity to comment on "Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge." 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)