



July 2nd, 2004

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

Re: Docket No. 2004D-0188, Federal Register: May 5, 2004 (Volume 69, Number 87, Page 25130-25132)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Draft Guidance for Industry: Development and Use of Risk Minimization Action Plans.

General Comments

BIO shares FDA's interest in providing timely access to patients with products that are safe and effective and to the healthcare system with information about products that emerges after the products reach the marketplace. Along with consideration of the benefits afforded by products, it is very important to minimize the occurrence of avoidable adverse events. Thus, risk management activities

should not impede distribution of or access to medicines for appropriate patients. In general, BIO believes that the draft Guidance reflects these goals, particularly the ultimate goal of ensuring that risk management efforts are evidence-based and that they achieve a positive balance of benefit and risk for individual patients and for target populations.

We note that the draft Guidance is based on the concept paper that was published last year (68 Federal Register 11120; March 7, 2003) and we applaud FDA's efforts to incorporate comments made by stakeholders at the public meeting on April 9-11, 2003, and also comments filed to Docket 02N-0528. We are in strong agreement with acknowledgment in the draft Guidance that Risk Minimization Action Plans (RiskMAPs) are to be used sparingly and only when a serious issue has been identified; the majority of marketing applications should not require a RiskMAP. We believe that this latter point should be explicitly stated in the Guidance document. In addition, RiskMAPs should be used to minimize risk in ways that do not inhibit access to products by patients who would benefit from them. Indeed, patient access to newer products should not be dampened merely because a RiskMAP is in place. We believe restricted distribution is an extreme measure and should be described in the final Guidance as a measure of last resort.

The aim of the draft Guidance is to encourage transparent, evidence-based risk assessment for all products. We commend FDA for this approach; however, in certain instances, we believe that it is impractical to expect small companies to implement certain tools on a broad scale to meet RiskMAP goals and objectives. As implementation strategies are considered, BIO members would like to work with FDA on approaches that would have the greatest impact on the public health and that can be effectively executed by large-, medium-, and small-size organizations. We believe that the goals and objectives of each RiskMAP should be customized for the specific situation, with a goal of focusing on a specific area of concern while avoiding unnecessary burdens on stakeholders for risk management activities. Nevertheless, global consistency is essential to achieve the intended results of RiskMAPs. Since many BIO members operate in more than 36 regulatory jurisdictions, we believe that it is essential for the draft Guidance to be consistent with international consensus group recommendations, such as those of the International Conference on Harmonisation (ICH) and the Council of International Organizations of Medical Sciences (CIOMS). For example, the Guidance on RiskMAPs should be consistent with the ICH E2E guideline (Pharmacovigilance Planning; 69 Federal Register 16579; March 30, 2004). Divergence from international consensus agreements has the potential to adversely impact data analysis and presentations, document presentations, and would require significant additional resources. Regional dilution of resources and a fragmented approach to risk management for a given product could reduce the benefit of RiskMAPs to the public health and make the impact more difficult to measure. Although FDA is committed to greater harmonization, we believe the steps to implement such proposals vis-à-vis RiskMAPs should be clearly defined in the Guidance.

Specific Comments

1. In general, products used for the treatment of life-threatening diseases may have identified safety risks that are not considered to impact negatively on the balance of benefits and risks. Such products usually have extensive phase IV commitments and often include the use of independent data safety monitoring boards. FDA is frequently involved in the decision to set up such monitoring boards. We believe the complexity of the existing proposal for RiskMAPs

for products with known serious safety concerns may have an undesired net effect, which will be an increase in cost without a commensurate benefit to the public health for existing products.

2. It is not possible to confirm the eventual safety profile of therapeutic products or vaccines with certainty before they are marketed. The detection of adverse events following introduction of a new product is highly dependent on the recognition and reporting of adverse events by health care professionals. The number and variety of safety reports and lack of reliable usage information makes it difficult to identify safety concerns from spontaneous reports because variability in the specificity of the safety information reported and the “noise” factor may mask potential signals.
3. The complexity of evolving changes in healthcare practices means that multiple healthcare providers, who frequently do not have complete access to the medical history of patients, often treat the same patient. This increases the chances for untoward events. The guidance to involve other healthcare stakeholders, including patients, in the spontaneous reporting and active follow-up of adverse events is of unproven usefulness. Hence, we believe FDA may have to take the lead in any proposal to improve the integration of healthcare systems if RiskMAP goals are to be achieved.
4. To meet the requirements contained within the draft Guidance, industry may need to establish and maintain entirely separate databases to continue to comply with existing global requirements and to comply with the new FDA requirements.
5. BIO believes the detection of relatively rare adverse events may have a significant impact on the public health. This is a fundamental aspect of risk management activities that have the goal of improving stakeholder understanding of the benefit-risk equation. The draft Guidance proposes various methods for improved detection using evidence and science-based risk analysis and management. However, BIO is not certain that the proposals would have a greater chance of detecting rare adverse events than the systems that are currently in place for pharmacovigilance monitoring and assessment.
6. The concept of a RiskMAP is introduced with the aim of ensuring that the risks of a product are outweighed by the benefit to the patient. A RiskMAP may be required, depending on the nature and rate of the known risks versus benefits, the preventability of the event and the probability of benefit. The tools for achieving the goals and objectives of the RiskMAP include targeted education and outreach, reminder systems, and performance-linked access systems. Some of these suggestions are well taken; however, we believe they are not practical because extensive resources may be required without a clear benefit over existing procedures.
7. RiskMAPs are intended for products with identified serious safety risks. Serious and labeled adverse events may be minimized or avoided by preventive measures. However, industry strives to use appropriate labeling, including updates to the label when warranted, and provides educational materials and academic detailing to health professionals as a mechanism to highlight risk. BIO does not believe that for targeted safety signals RiskMAPs will be any more effective than existing processes at reducing the occurrence of the event of interest as, in many instances, defined post-approval regulatory commitments include proposals for risk identification and management.

8. The development of effective RiskMAP tools remains a challenge. The literature does not suggest that exposing practitioners to additional education, or that the use of prompts and reminder systems provides long-term and sustained changes in the behavior of healthcare professionals that is necessary to achieve the goals and objectives as outlined in the draft Guidance. Indeed, we believe the proposal regarding certified practitioners, pharmacies, registration and evidence of safe use conditions would likely restrict availability of needed products. Further, this concept seems to inhibit the practice of medicine and may not be willingly accepted by healthcare professionals.
9. Targeted education and outreach, reminder systems, and performance linked access systems (link product access to lab testing or other documentation) are entirely new requirements and will require extensive pre-testing, post-testing, and validation to achieve the desired effect in an efficient manner. This validation approach will be required for all products and will add a considerable expense burden to marketing of new products.
10. Consultation with practitioners and patients on feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions or lifestyles will be a major and time consuming exercise. FDA proposes that sponsors should use the least burdensome tools necessary to achieve risk minimization. However, the response from busy healthcare professionals may be less than optimal and it is unlikely that RiskMAPs will elicit high levels of compliance. Quantifying the outcome of a RiskMAP is complex and may depend on accessibility to information, privacy concerns, good database systems, and quantitative analysis skills. The development of prospective plans to delineate which RiskMAPs may be acceptable to a company, FDA, and also to practitioners, will be affected by the specific disease indication, availability of alternative therapies, outcome measures, etc. Also, determination of the acceptable level of compliance will be time-consuming and practitioners may feel that these measures are being forced upon them; they may not agree that the RiskMAPs are required. Thus, compliance and diligence in providing the relevant information to FDA may be less than optimal. We recommend FDA consider more practical alternatives that may include enhanced labeling, greater participation in education programs, and ways to make product information more accessible, etc.
11. Although FDA recognizes that the traditional risk minimization tools have had limited effectiveness (changes in prescribing information and Dear Healthcare Professional letters), the draft Guidance does not directly outline ways in which the appropriate behavior changes in the broader healthcare system can be effected. However, the draft Guidance does suggest that well-designed, evidence-based, and objective performance measures should be introduced for effective performance assessment and evaluation of RiskMAPs. Similar performance measures are proposed to measure effectiveness of the tools. These measures will demand greater participation and intervention from healthcare professionals and will require that sponsors use multiple evaluation methods and regular evaluation of RiskMAPs, e.g., pretesting/validation/post-testing and progress reports.
12. RiskMAP requirements, if perceived as onerous, could steer healthcare providers or patients to older therapeutic regimens that have a less favorable benefit/risk profile than one with a RiskMAP. Thus, many BIO members believe that it is critical for FDA to create and sustain a predictable regulatory environment regarding RiskMAPs. The circumstances for which additional risk assessment and risk minimization activities would be indicated should be completely transparent so that patient access to new effective therapy is not jeopardized for all

or a subset of the target population. We strongly encourage FDA to include wording in the Guidance that, depending on personal preferences, disease, stage of disease, prognosis, or aggressiveness of the disease, some individuals may wish to trade more risk for more or less benefit. If used effectively, a RiskMAP can enable that tradeoff for individuals by recognizing those personal preferences.

In conclusion, BIO endorses the concept of managing risk relative to potential benefit for populations and for individuals. We look forward to additional dialogue with FDA to clarify outstanding concerns regarding RiskMAP creation, implementation, and reporting. We believe that this dialogue is essential to optimize the intended benefit of RiskMAPs. Our shared goal is to minimize risk to patients while ensuring that safe and effective biologic products will continue to be developed and marketed to meet unmet medical needs in appropriate individuals and target populations.

Sincerely,

A handwritten signature in cursive script that reads "Sara Radcliffe".

Sara Radcliffe
Director
Science Policy and Bioethics