BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

June 19, 2008

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Docket 2008N–0257: Draft Prescription Drug User Fee Act IV Drug Safety Five-Year Plan; Availability for Comment

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on *The Draft Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-Year Plan.* BIO applauds FDA for outlining the agency's efforts to establish a comprehensive approach to prescription drug evaluation across a product's lifecycle and further enhance FDA's ability to balance the benefits and risks of medical products in the post-market setting.

BIO represents more than 1,200 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 technologies, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

The PDUFA IV Drug Safety Five Year Plan represents a critical component of FDA's efforts to modernize the agency's post-market surveillance and benefit/risk management activities, consistent with the new authorities and resources authorized under the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-085) and the

PDUFA IV Technical Agreement for FY08-FY12. BIO supports a capable, science-driven FDA that has the resources necessary to keep pace with rapidly evolving biomedical science and make sound regulatory decisions in a timely and efficient manner, and commends FDA's acknowledgement of the need to build scientific and administrative capacity to achieve the objectives highlighted in the PDUFA IV Drug Safety 5-Year Plan. Overall, BIO believes that there are a number of useful initiatives outlined in this document and that the plan will help to further clarify the new authorities and responsibilities resting with the agency since the passage of FDAAA legislation.

BIO is pleased to offer the following general comments in support of the 5-year plan:

- *PDUFA Drug Safety Activities Should Be Aligned with the Agency's Overall Efforts to Implement a Lifecycle Approach to Medical Product Evaluation:* BIO supports the initiatives established under PDUFA IV to improve FDA's drug safety activities, such as improving collection and analysis of adverse event (AE) data, enhancing proprietary name evaluation, and developing best practices for RiskMAPs and epidemiological studies. However, these PDUFA drug safety activities are only a small part of FDA's comprehensive effort to establish a full lifecycle approach to medical product evaluation through strategic initiatives such as *Safety First*, *Safe Use*, and the *Sentinel Initiative*. BIO encourages the agency to frame these PDUFA initiatives within the context of this larger strategy so that companies and the general public can better understand how a single initiative will contribute to FDA's overall evaluation of a product across its lifecycle – from pre-market development to NDA/BLA review to the postmarket environment.

- *More Specificity is Required so that Industry Resources can be Aligned to Support the Proposed Changes:* Efforts to ensure that prescription drugs improve our nation's drug safety and pharmacovigilance systems will require substantial investments and changes in business practice from the FDA, industry, pharmacists, practitioners, and many other stakeholders in the U.S. healthcare sector. If this plan is to serve as a strategic plan or "roadmap" to help both FDA and external stakeholders to align their resources towards successful implementation of the FDAAA and PDUFA drug safety goals, the plan would benefit from greater specificity that details the underlying strategies, timelines or milestones, and the resources (personnel, funds) necessary to achieve each objective.

- *Global Harmonization*: BIO member companies conduct business in the global marketplace, and wherever possible and appropriate encourage the international harmonization of regulatory requirements. Pharmacovigilance and benefit/risk management are global undertakings and as such, should be addressed from both a domestic and international perspective. Global harmonization of key initiatives should be a goal so that overall FDA and industry resources expended on safety can be efficiently utilized.

- *The Plan Should Address Additional Fee-Funded Activities Authorized under FDAAA:* User fees play an important role funding certain targeted FDA activities and significant new fees were directed under the PDUFA IV technical agreement to fund FDA's post-market surveillance activities. However, during Congressional deliberation of the legislation, an additional $225 million over 5 years in industry user fees was authorized to fund unspecified drug safety activities. Given these significant additional fees, BIO believes that the agency should use the 5-year plan as an opportunity to provide greater specificity on how these additional FDAAA-authorized user fees will be expended in order to implement the agency's comprehensive drug safety strategy. For example, we suggest that FDA outline how the FDAAA-authorized user fees will be used to implement the labeling review process for managing safety labeling changes, and will be used to ensure timely REMS review.

SPECIFIC COMMENTS:

BIO is pleased to offer the following specific comments in support of the 5-year plan:

6.1: Strengthening Management and Operations

In the plan and in recent press releases, FDA has announced that they must hire and train several hundred new staff to meet the FDAAA and PDUFA IV requirements. Given that training a new staff member can take 2-3 years, we request that FDA outline its plan for prioritization and handling of responsibilities in the interim.

Given the need for increased staff and the apparent shortage of drug safety professionals, how will the agency compete for experienced professionals? Once FDA attracts new professionals, what educational programs are in place to train them? Additionally, there needs to be more clarity regarding roles of FDA staff vs. external consultants. For example, will the FDA maintain in house expertise in signal detection and analysis of AE data or will this primarily be performed by external consultants and/or collaborations?

6.2: Improving Collection and Analysis of Adverse Event Data

Industry expends considerable resources conducting AE collection and analysis. BIO was pleased that FDA held a recent workshop on improving AE collection and analysis to solicit stakeholder input and BIO believes that it will be beneficial for the agency to continue to develop its strategy in collaboration with industry. This would avoid duplication of effort as well as limit confusion on the part of AE reporters. In particular, we request that FDA specify the criteria that will be used to assess the methodologies for collecting AE information at various points in a product lifecycle. Additionally, given the limitations of spontaneous reporting, any new strategies or methodologies for surveillance based on spontaneous reporting should be carefully evaluated and tested before full implementation.

Also, it is in the best interest of patients that the drug and biologic sponsors have access to all of the information necessary to understand the evolving benefit/risk profiles of their

products. Thus, any information that the FDA obtains that would add to that knowledge should be made readily available to the sponsors, to the extent possible, without the need for Freedom of Information requests.

Finally, we note that the timing of this initiative has not been described. The research approach described will result in a rather prolonged process. We suggest that at the very least, a communication plan should be provided/planned to advise the industry and the public regarding the progress of the initiative. It would be preferable for the agency to provide a timeline for implementation of the plan.

6.3 Implementing Epidemiology Best Practices

BIO supports the Agency's efforts to fully utilize new electronic health care data sources for post-approval pharmacoepidemiologic studies. These new data resources offer great promise to revolutionize the practice of pharmacovigilance with more timely and cost-effective methods for conducting Phase IV studies, but great care must be taken to minimize the potential for biases. BIO echoes the sentiment expressed at the May 7th public workshop that standards and best practices must be developed to address key issues such as data quality, database validation, study design and validation, data access, governance, and personnel qualifications. We believe it is important to understand how these studies will be interpreted given their potential for bias and encourage FDA to clarify the burden of evidence required to take regulatory action based upon pharmacoepidemiological database studies. We also request that FDA provide information about whether the determination of epidemiologic best practices will be a U.S.-focused or a globally-focused activity. While we appreciate that the FDA's mandate directly relates to the U.S., we believe it is reasonable to also include EMEA and APAC regions in data gathering and further considerations of the complex issues associated with the development of pharmacoepidemiological best practices.

While BIO supports the development of guidance on safety studies using large electronic healthcare databases, we note that FDA has three years to issue a final guidance, consistent with the PDUFA IV performance goals. We encourage FDA to shorten this timeline and issue a final guidance before three years have passed. If this is not possible, we would encourage the agency to consider what preliminary advice the agency will offer medical reviewers, academia, and industry in the interim period as these types of database analyses become increasingly common.

6.4 Expanding Database Acquisition and Use for Targeted Post-Marketing Surveillance

BIO supports FDA initiatives to implement a targeted, active surveillance infrastructure and views the recent *Sentinel Initiative* report as a promising step in that direction. However, this section of the plan only lists the data sources that FDA has used in the past and some that the agency will use in the future, but does not detail any particular strategy for utilizing the databases in a coherent, focused manner to maximize the quality of any resulting analyses. We request that there be more detail on how these data sources will be used and how the agency will validate the outcomes of interest.

Also, we ask FDA to confirm that it will disclose which analyses from these databases were used to support regulatory decisions.

6.5 Strengthening Risk Management and Communication Tools

Risk management and risk communication are critically important areas, particularly in light of changes made under PDUFA IV and FDAAA, and merit additional discussion in this section. We support increased globalization and standardization of risk management requirements, documentation, tools and updates across individual health authorities. At present, the definitions, format and scope for FDA classification of risk evaluations (Risk Evaluation and Mitigation Strategies (REMS) and Risk Minimization Action Plans (RiskMAPs)) vs. those of the European Medicines Agency (Risk Management Plans) are not clear. For example, given the increasing complexity of labeling and the need for proactive risk management planning, a summary of risk management for a product may be required by the FDA. In this situation, we support that the written information should be similar in content and format to the EU-Risk Management Plan (either for new NDA/BLA submissions or postmarketing submissions for significant changes to product, e.g. new indications).

We look forward to publication of the forthcoming FDA guidance on format and contents of a proposed REMS and BIO encourages FDA to address what will be required under a REMS (e.g., format/template/acceptable examples), as well as detail the pathway for evaluation and approval of individual RiskMAPs or REMS within FDA. REMS elements are statutorily defined in FDAAA and include some overlapping components of RiskMAPs; additional clarification from FDA on the distinction between REMS and RiskMAPs would be welcome. We also request that FDA clarify the intersection of the REMS regulations and other areas of law, including but not limited to, the Health Insurance Portability and Accountability Act (HIPAA) and state privacy laws (requiring a manufacturer to ensure capture of patient level information, reaching out to the patient if necessary), corporate practice of medicine and product liability (requiring manufacturer to assess the quality of physician's diagnosis as to on or off label), misbranding (directed distribution by manufacturer to off label patients), and off label promotion (including off label REMS information in REMS tool kit increasing risk of FDA interpretation as off label promotion).

In addition, sponsors are currently being asked to institute various programs to impose restrictions on utilization, including using mandatory registries, reminder systems including informed consent, and other tools with the goal of limiting off-label or inappropriate use. We agree with the need to assess and validate the utility of such tools. However, we encourage evaluation of the impact of these programs on health care providers, the practice of medicine, and the barriers that these programs may create to patient access from all stakeholders.

We welcome FDA's interest in holding public workshops and advisory committees to solicit stakeholder input, but we also encourage the agency to focus on proactive strategic approaches. For instance, we suggest that FDA works with other stakeholders (industry, patient groups, medical societies, etc.) to improve the way safety risks are communicated

to health care providers and the public in order to allow them to make informed decisions about treatments.

Finally, we request that dates or milestones be provided in this section.

6.6 Improving Post-Market Information Technology Systems
Information technology enhancements to support new post-market safety systems will pose significant technical and management challenges for both FDA and industry. We encourage FDA to engage external stakeholders early in the process of defining these systems to ensure adequate time for the strategic planning necessary to adopt new data standards and migrate to new systems. We also ask for more information on these initiatives to ensure that industry resources are being expended in sync with the direction that the FDA is taking.

Additionally, we ask FDA to clarify the impact of the MedWatch Plus and the MedWatch Plus portal on the electronic submission functionality and industry IT and support expanding FDA Adverse Event Reporting System (FAERS) to include electronic receipt of safety information from a variety of sources, including periodic reports. We believe there should be bidirectional flow of information from a company to FDA, and FDA back to that company. Further, we ask FDA to ensure that companies have access to FAERS and the Sentinel System so that we can include this data in our internal surveillance. Again, we encourage global harmonization efforts in these areas as well.

CONCLUSION:

BIO appreciates this opportunity to comment on *The Draft Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-Year Plan*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director for Science and Regulatory Affairs
Biotechnology Industry Organization