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

Re: Docket No. 2007N-0480: Maximizing the Public Health Benefit of Adverse Event Collection throughout a Product's Marketed Lifecycle

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) wishes to thank the Food and Drug Administration (FDA) for the opportunity to submit comments on *Maximizing the Public Health Benefit of Adverse Event Collection throughout a Product's Marketed Lifecycle*, and for its inclusion of BIO as a representative stakeholder. BIO supports the FDA's initiative to study the agency's current spontaneous adverse event (AE) reporting system and offers the following research topics for inclusion in FDA's Request for Proposal (RFP). Research to identify the core strengths of the spontaneous reporting system will help to more efficiently allocate limited FDA and health sector resources to enhance the value of passive reporting and develop complementary signal detection systems, such as active surveillance, to further promote the public health.

BIO represents more than 1,150 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, enhance agriculture, and a cleaner and safer environment.

Patient safety is an integral and paramount part of BIO member companies' considerations during research, clinical development, and continued post-marketing evaluation. All drugs and biologics carry both benefits and risks that should be carefully weighed by patients and their doctors. Patients and physicians need timely, accurate, and relevant information about the benefits and risks of a drug or biologic so they can make well-informed choices about therapy. Spontaneous adverse event reporting is an important, albeit limited, source of information to help further characterize a product's benefit/risk profile and should be enhanced to maximize its core strengths.

THE VALUE AND LIMITATIONS OF SPONTANEOUS REPORTING:

The spontaneous adverse event reporting system serves a significant public health function, i.e., to help to identify potential safety signals that may not be readily apparent in pre-market clinical trials or those that emerge after approval. Spontaneous reporting is most useful to identify safety signals where the event of interest is clinically well defined and distinctive, the background rate of the event is low, and it is possible to draw a close temporal link between the event of interest and exposure. The association between thalidomide exposure and the distinctive birth defect phycomelia is a classic example. The system also provides valuable information on "real-world" utilization of medical products and may help identify associations that are not apparent in clinical trial settings and controlled patient populations.

While spontaneous AE collection is useful for the identification of some safety signals, the information is often not sufficient to detect safety signals and only rarely sufficient to confirm safety signals. For certain types of safety issues spontaneous adverse event reports are inherently of limited value. These safety issues include common clinical symptoms or syndromes, adverse drug reactions with long latent times such as carcinogenesis, and adverse events which are indistinguishable from the natural history of the indication. We recommend that the RFP request proposals relating to the following research questions.

- *Research Proposal:* For which types of safety issues is spontaneous adverse event reporting more and less valuable?

- *Research Proposal*: Would stratification of the Adverse Event Reporting System (AERS) database by type of safety issue increase the chances of identifying or better characterizing new safety signals? What would be the effect of removing certain types of safety events (those for which spontaneous reporting is known to be of very limited value) from AERS?

We note that both the FDA and the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) have explored the idea of specific types of adverse events which should always be considered serious.

- *Research Proposal*: What are the implications of focusing adverse event reporting on "serious" issues? We note that it may be possible to model such an approach using information currently available in the AERS system.

Additionally, we note that while spontaneous reporting databases can be useful for generating hypotheses, other data sources such as clinical trials and active surveillance are often necessary to detect safety signals and confirm true cause-and-effect relationships. Benefit/risk communication is also essential to complement these various methods for detecting and confirming safety signals, in order to create a comprehensive approach to post-market surveillance.

"ACTIONABLE" DATA SOURCES:

We recommend that FDA seek input on how to stratify adverse event data to determine which sources of data produce the most constructive, actionable information for taking regulatory action. The RFP should ask how we can maximize reporting and follow-up from those sources, while minimizing inefficiencies generated by follow-up from less useful sources. For instance, are certain types of safety signals more likely to be detected through AE reports from patients? What factors influence the distribution of AE reports by source? Does the pattern change over time?

- *Research Proposal*: Would stratification or restriction of the AERS database by report source increase the chances of identifying or better characterizing new safety signals?

ADVERSE EVENT COLLECTION ACROSS A PRODUCT'S LIFECYCLE:

We recommend that FDA seek input on how the value of spontaneous reporting varies across the various phases of a product's lifecycle. Many of the most significant safety signals are detected in the period immediately after product approval when the product is introduced in larger and more diverse patient populations. Other important safety information can be detected late in a product's lifecycle, but there may be diminishing utility in reporting certain data elements for older, better characterized products. BIO supports the initial analysis conducted by FDA's Office of Surveillance and Epidemiology (*McAdams et al, 2007*) examining the association between the time since product approval and subsequent regulatory action. This study represents a promising basis for future research to determine the association between the time since approval and the confirmation of new safety information.

- *Research Proposal*: Would stratification or restriction of the AERS database by time since approval increase the chances of identifying or better characterizing new safety signals?

QUALITY, NOT QUANTITY:

It is generally recognized that adverse events are underreported in the current spontaneous reporting system. However, increasing the quantity of reports without improving the overall quality of reporting will likely produce the unintended result of generating noise and uncertainty, rather than knowledge and actionable intelligence. A handful of thoughtful, thorough, and communicative case reports can be more illustrative of a potential safety signal than hundreds case reports lacking completeness and consistency. There are very wide differences in quality, completeness and interpretability in adverse event reports yet these differences are ignored in many analyses, particularly in AERS data-mining approaches.

We recommend that under the RFP FDA explore the role played by the quality of spontaneous adverse event reports in providing useful information for the identification or confirmation of safety concerns and the integration of this information in analysis and evaluation. For example, is it possible to develop a model of quality of information for spontaneous AE reports that weighs aspects such as the completeness of the information, the precision of the diagnosis, the presence of information on concomitant medications, and other quality measures, and that would permit creation of a triage system so that reports are weighted by quality?

- *Research Proposal*: Can a system of weighted quality indicators be applied to case reports to determine whether higher quality case reports more often lead to regulatory action?

TERMINOLOGY IN ADVERSE EVENT REPORTING:

Working definitions of a new safety signals play a critical role in the timing of detection and characterization of a safety risk. Conflicting definitions and terminology can lead to major – but avoidable - difficulties in defining the scope an emerging safety signal. Specifically, parameters including MedDRA terms and coding conventions and the regulatory definition of "seriousness" can heavily affect the quality and quantity of AE reporting.

- *Research Proposals*: Examine case studies and/or conduct a retrospective analysis and simulation of the AERS data to determine the optimal AE "concept units" (such as MedDRA Preferred Terms, Standard MedDRA Queries) for the application of data mining and other analytical methods.

HEALTH CARE PROFESSIONAL EDUCATION AND WORKFLOW:

Educational efforts among health care professionals and streamlined reporting processes can also help improve the quality of AE collection. BIO supports efforts to incorporate adverse event reporting into medical school curricula and continuing medical education

(CME) programs to stress the public health importance of AE reporting among health care professionals. Special efforts should also be made to educate nurses and physician assistants who often submit reports on behalf of a practicing physician.

- *Research Proposal*: Conduct a literature review of previous outreach initiatives to healthcare providers aimed at improving adverse event reporting to identify the most successful strategies and interventions. Resources permitting, the most effective strategies should be regionally piloted and evaluated.

Additionally, the processes for submitting adverse event reports should be streamlined to improve workflow, decrease the administrative burden of reporting, and eliminate redundant reporting requirements. BIO is encouraged by the FDA's efforts to upgrade the MedWatch system to incorporate modern internet-based submissions, as well as the recent memorandum of understanding between FDA and the National Institutes of Health (NIH) to create a "rational" electronic questionnaire for AE reporting and a single web portal for AE reporting.

BIO would also encourage efforts to generate a list of targeted events upon which practitioners would be prompted to submit an AE report. As noted above in our comments on the value and limitations of spontaneous adverse event collection, both the FDA and the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) have explored the idea of specific types of adverse events which should always be considered serious.

COMPLEMENTARY SYSTEMS FOR ACTIVE SIGNAL DETECTION:

As mentioned previously, spontaneous reporting is proficient at identifying rare, well characterized adverse events, but the system is less suited for identifying increased rates of common adverse events that often blend into the background rate, such as cardiovascular events. Due to its inherent limitations, the spontaneous reporting system should not be expanded to attempt to capture all of these types of adverse events, but more modern approaches should be employed to detect safety signals typically missed by the spontaneous reporting system. An active surveillance system should complement FDA's passive surveillance capacity and provide FDA with additional tools and expertise to evaluate safety signals systematically and more quickly elucidate the relationship between drug exposures and unexpected adverse events. BIO supports the requirement in *The Food and Drug Administration Amendments Act of 2007* that FDA establish such a system of linked population based healthcare databases to provide information about safety concerns. Additionally, epidemiological studies and controlled clinical trials may be necessary in certain instances to further evaluate and confirm suspected safety signals.

- *Research Proposal*: Explore how the spontaneous reporting system and the active surveillance network can be mutually complementary. How and under what circumstances, for example, might the active surveillance network be used to evaluate safety signals generated by the spontaneous reporting system?

CONCLUSION:

BIO appreciates this opportunity to comment on FDA's initiative for *Maximizing the Public Health Benefit of Adverse Event Reporting*. Research to help identify how the agency can more effectively and efficiently conduct passive post-market surveillance to focus on the system's core strengths will allow the agency to reprogram funding to establish complementary signal detection systems and realize a comprehensive, 21st century vision of pharmacosurveillance. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

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