April 5, 2007

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

Re: Docket No. 2007N–0016, Sentinel Network to Promote Medical Product Safety

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment to the Food and Drug Administration's (FDA's) public meeting on the *Sentinel Network to Promote Medical Product Safety*. To date, biotechnology researchers and companies have created, tested, and brought to the market more than 200 new therapies and vaccines, including products to treat cancer, diabetes, autoimmune disorders such as arthritis, and HIV/AIDS. Developing and utilizing the best available scientific information about safety is an integral and paramount part of biotechnology companies' considerations across their medicines' lifecycles, from discovery through clinical development through the marketed life of the product.

BIO Supports an Active Surveillance System:

While the specific details of a "Sentinel Network" are yet to be defined, BIO supports the establishment of a private-public partnership to develop an electronic active surveillance system that can leverage the growing trove of health information contained in population-based medical databases, payer systems, and electronic health records (EHR). Signal detection strategies, including surveillance reporting systems, pick up early manifestations of what could potentially be a drug safety problem. The term "Sentinel" emphasizes the initial signal detection, but the system should also include the additional dimension of risk assessment, evaluation, and communication. A fully integrated active

surveillance system could more efficiently and effectively gather safety information after drugs have been approved for marketing; develop new tools and methodologies to analyze emerging safety data; and communicate the benefits and risks of prescription drug products to patients and physicians. Such a system could better inform individual medical decisions made by patients and physicians, improve patient outcomes and quality of care, and help to restore a high level of trust in the FDA and regulated industry.

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. FDA's MedWatch spontaneous reporting system is good for identifying unusual drug-related serious adverse events, but contains limited information from a snapshot in time in many cases. Limitations in the passive surveillance system make testing safety hypotheses difficult, but a linked network of population-based medical databases would provide additional capacity so that unanswered questions about the safety of medical products could be answered in a more timely manner.

A number of current surveillance systems, such as the National Nosocomial Infection Surveillance System, the National Vaccine Safety Datalink, FDA's own MedSun device initiative, and European surveillance systems, provide valuable insight and experience and have demonstrated that active surveillance systems can be established through current technology. FDA's pilot program of active surveillance using linked pharmacy-medical claims also provides important support for the utility of such systems in the identification and assessment of safety concerns.

Biopharmaceutical Industry Expertise Should Be Harnessed to Build an Active Surveillance System:

Many stakeholders, particularly the biopharmaceutical industry, are interested in working together to build a comprehensive, fully operational active surveillance system. It is difficult and duplicative for any individual manufacturer to develop broad, reliable, population-based systems for gathering further evidence on the use and effects of drugs in clinical practice. In certain instances, an active surveillance system would obviate the need for individual companies to establish separate Phase IV databases, and would better direct limited resources to conduct necessary randomized, controlled trials.

An active surveillance system utilizing integrated health data to assess safety signals and other safety concerns could create a very rich, but qualitatively different resource for safety evaluation. Beyond the technical issues are questions of governance. How should such data be used, by whom, and to answer what questions? What level of validation is required at the level of the system as a whole? What level of validation and review are required to evaluate individual safety issues. How, and by whom, are the results of such assessments vetted and communicated?

Involvement of the pharmaceutical and biotechnology industries in this process is critical. Data generated from such tools should be evaluated in the context of the full set of information on the product. Risk identification, analysis, and communication require a full understanding of the information available about the product and safety problem addressed. The contribution of the expertise of these industries and their long term experience in the area of patient safety will allow a more rapid maturation of the network.

Current Challenges and Proposed Solutions to Developing an Active Surveillance System:

Several significant challenges and obstacles must be overcome to realize the vision of an electronic active surveillance system for medical products.

Data Quality: An active surveillance system may provide additional post-market surveillance capacity, but the resulting analyses will only be as good as the quality of the source data. Various data sources that an active surveillance system would utilize, including as electronic health records, are not designed for the purpose of product safety evaluation. EHRs have issues of data validity and subtle, but important, potential bias can be present. Evaluation of these issues is central to the use and acceptance of findings generated by an active surveillance system. For example, claims databases, coding patient diagnoses, and treatments on the ICD-9 codes are devised for reimbursement purposes rather than to track medical outcomes. Moreover the accuracy and completeness of information may vary by product, by disease and by the EHR system. Any risk analysis based on EHR must include a validation component specific to that issue and data set.

To facilitate reporting of well documented suspected adverse drug reactions, the development of electronic health records should incorporate some form of electronic reporting capability that will allow a provider to automatically capture relevant patient information, such as medical history, pharmacy records, and lab data, with only minimal additional data entry and electronically submit the report to FDA. To improve the quality of data collection at the point of care, the post-market safety data collection should be integrated into the workflow of clinical practice at the point of care in a manner that does not impose burdens on health care providers, patients, and health care institutions. A first step might be to automate the collection of adverse event data from existing electronic medical records to decrease the administrative burden of data collection. A promising example of this type of standardized information re-usability among business partners is Clinical Data Interchange Standards Consortium (CDISC) “retrieve form for data capture demo.”

Standards, Interoperability, and Semantics: For a fully functional and integrated active surveillance system to operate, significant issues relating to standards, interoperability, and semantics must be overcome. Without established data standards, FDA and stakeholders will be unable to integrate and communicate between their respective systems. Currently, information technology knowledge and infrastructure

differ by institution, but common standards would streamline the process and minimize potential burden. The standards utilized should be nationally and internationally harmonized and forward-looking so that systems can incorporate both currently available data sources and emerging electronic health records.

In addition, there must be established semantics and definitions for adverse event collection and medical outcomes for data sources to be pooled and integrated. BIO notes that FDA and international regulators require the Medical Dictionary for Regulatory Activities (MedDRA) for coding adverse event reports, while the Systematized Nomenclature of Medicine (SNOMED) is used for coding physician label highlights and electronic medical records. An active surveillance system would benefit from standard, harmonized definitions for identification and coding of adverse drug reports.

Data Analysis: An active surveillance system must not only be able to integrate various data sources, but the methods used to analyze the data must be governed by good epidemiologic practices. Some analytical processes can be automated to generate possible safety signals, but output from such techniques needs to be carefully evaluated to identify false positive results. There should also be an efficient adjudication system to resolve disputes among stakeholders to determine when safety signals are in fact significant.

On the other hand, evaluation of specific predefined safety issues is often complex and requires the use of sophisticated methods of adjustment to minimize the effects of confounding. Study design requires considerable expertise and the attention of medical officers and epidemiologists is essential to interpret the data. Access to the original medical record is critical if key results are to be confirmed.

Benefit/Risk Communication: Ultimately, an active surveillance system will serve little purpose if benefit/risk information is not appropriately communicated to the public in a clear and consistent manner. The surveillance system can help to provide patients and physicians with timely, accurate, and relevant information about the benefits and risks of a drug or biologic so they can make well-informed choices about therapy. A framework should also be developed to articulate how the data is used and communicated. Not only must FDA weigh what information to communicate, what audience to communicate with, and what medium to use for communication, but also when in the ongoing data analysis it is appropriate to communicate.

Piloting and Validation: New tools and methodologies should be appropriately validated and BIO urges FDA to coordinate with partners in industry and academia early in the process to pilot data systems in advance of any system activation. Each element of an integrated active surveillance system should be properly validated at each step of the process – from data collection to analysis to communication. FDA should contract with external organizations, consultants, and vendors to validate and benchmark the operational success of the surveillance systems.

Governance and Stakeholder Access: Prior to the creation of a private-public partnership to develop an active surveillance capacity, FDA should establish an

appropriate governance structure that would allow participating stakeholders and experts to help set priorities and recommend future research activities. In order to solicit adequate private sector participation, FDA should also thoroughly clarify who will have access to and ownership of the collected data and analyses.

Privacy and Proprietary Information Concerns: Patients must be assured that their privacy, and the confidentiality of any medical information collected, will be protected. Patients should be made aware that all data collection and management is compliant with the Health Insurance Accountability and Portability Act (HIPAA). With appropriate safeguards for privacy and confidentiality, however, it should be possible to identify patients if original records or missing data need to be retrieved.

In the longer term, it is critically important to collect and analyze medical information in order to improve the quality of medical care offered in the United States. The Federal Government is properly situated to stimulate a public dialogue on when and what type of individual authorization is necessary for the collection of private medical data in order to gain significant advances in patient safety and public health.

Additionally, the system should take into account proprietary considerations for brand products to achieve appropriate levels of information security, confidentiality and privacy.

Financial Obstacles: Creating an active surveillance system will require additional financial resources from private and public sources. However, the cost of creating this system, if it is well-designed, will be more efficient due to the economies of scale involved than individual drug-by-drug risk management strategies conducted by drug manufacturers. A structure should be implemented that will allow the system to receive funding from both private and public sources. There are a number of examples of such privately and publicly funded partnerships, including the C-Path Institute and the Biomarkers Consortium. Besides providing overall financial support for such a system, the costs of analyses to address special issues will need to be addressed.

Short Term, Small-Scale Projects: In the near term, a "federated model" that harnesses current data systems and multiple surveillance tools can be utilized. These include projects under the FDA-Veterans Administration Memorandum of Understanding, Centers for Education & Research on Therapeutics (CERTs) programs, and the previously cited FDA contract program utilizing proprietary databases which link pharmacy and medical claims. These smaller scale initiatives may help to define and test issues surrounding governance, access to data, interpretation of results, and communication of findings.

Conclusion:

BIO appreciates this opportunity to comment on FDA's public meeting on the *Sentinel Network to Promote Medical Product Safety*. We look forward to assisting FDA towards

the development of a 21st Century post-market surveillance capacity which if implemented correctly will allow safe and efficacious medicines to reach patients faster and improve the monitoring of the benefits and risks of drugs and biologics across their lifecycle. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director
Science and Regulatory Affairs