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March 27, 2009

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

Re: Docket No. FDA-2008-N-0612, OC 2008312. Sentinel Initiative: Structure, Function, and Scope; Public Workshop

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Sentinel Initiative: Structure, Function, and Scope. 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 products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO supports the development of a national, integrated, electronic system for monitoring medical product safety that can leverage the increasing availability of electronic health information contained in population-based medical databases, payer systems, and electronic health records (EHR), so long as the system is designed and operated to provide useful medical information in an open and transparent manner. [1,2] BIO

[1] BIO Comments on "FDA's Sentinel Network to Promote Medical Product Safety" (April 5, 2007), http://bio.org/reg/20070405.pdf

[2] BIO Comments "Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets" (June 6, 2008), http://bio.org/reg/20080606.pdf

commends the FDA for its deliberate, consultative, and step-wise approach to implementing the Sentinel Initiative and we encourage additional consultation before the program is finalized. We agree with the Agency that the implementation of the Sentinel Network should be an evolutionary process and that there are many areas that require further development and clarification around how exactly these large-scale administrative databases will be used as tools to ensure and improve public health. Further, BIO is committed to applying its expertise and the expertise of its member organizations in collaboration with the FDA and other stakeholders to work through both the challenges that already have been identified as well as those that may arise in the future in developing this important capability.

I. PUBLIC PARTICIPATION & GOVERNANCE:

As FDA has demonstrated in its December 2008 public workshop, a guiding principle of the Sentinel Initiative must be broad and diverse public participation throughout the development and use of the network. Implementing the system poses significant technical, privacy/legal, and scientific issues that can best be addressed through public consultation and dialogue. BIO is pleased that the FDA is committed to soliciting additional public feedback on Sentinel-related white papers and other implementation documents through the standard Federal Register notice-and-comment process. BIO member companies have significant in-house expertise relating to pharmacoepidemiologal methods and post-market surveillance and we intend to continue to provide constructive feedback during Sentinel Network implementation.

In addition to soliciting general public input, it will be critical to establish a formal governance mechanism for the Sentinel Network to leverage expertise and insight from a broad range of stakeholders. A promising model for this type of private-public partnership has been the American Health Informatics Community (AHIC), a federal advisory body chartered in 2005 to make recommendations to the Secretary of the U.S. Department of Health and Human Services on how to accelerate the development and adoption of health information technology. AHIC is comprised of 18 voting members serving two-year terms representing a multi-disciplinary team of government officials and private sector experts and leaders. AHIC working groups were established to address specific sub-topics.

An AHIC-style governance model would be appropriate for the Sentinel Initiative to help promote public confidence in the project, establish by-laws and operational policies, and identify areas for future research or expansion. Membership could be comprised of key government officials (HHS, FDA, CDC, CMS, VA, DoD and other agencies) and private sector stakeholders such as manufacturers, data owners, patient advocates, medical providers, academic researchers, and public health experts. This type of private-public partnership could be established under the auspices of the Reagan-Udall Foundation for the FDA which is authorized under the FDA Amendments Act of 2007 to “enter into contracts, memoranda of understanding, or cooperative agreements with, scientists and entities, which may include the Food and Drug Administration, university consortia, public-private partnerships, institutions of higher education, entities described in section

501(c)(3) of the Internal Revenue Code (and exempt from tax under section 501(a) of such Code), and industry…" (21 USC § 379dd(c)(4)).

Additionally, it will be important that the governance structure have a dedicated division responsible for commissioning research around pharmacoepidemiological methods and validating those methodologies. As the state of the science and technology advances, a governance subgroup comprised of subject matter experts should provide guidance on future research and make recommendations on adoption of the latest available tools and approaches.

II. FINANCING:

To be successful, the Sentinel Initiative must receive adequate resources to hire staff and researchers, enter into contracts with data owners, and develop technological infrastructure. However, to preserve the independence and credibility of the Sentinel Initiative, it is also important that those resources come from balanced mix of public and private sources.

As a founding member of the *Alliance for a Stronger FDA*, BIO has successfully advocated for significant new appropriations to modernize FDA's post-market drug evaluation systems. We hope that a considerable portion of those appropriated funds will be directed towards the Sentinel Initiative. Indeed, Congress specifically authorized up to $25 million for the activities authorized under Section 905 of FDAAA, which includes FDA's efforts to establish an active postmarket risk identification and analysis system. We will continue to encourage Congress to appropriate additional funds for Sentinel, and we trust that FDA will spend drug safety funds on the Sentinel Initiative. We also recognize that industry user fees can play a role in supporting elements of the initiative. For example, under PDUFA IV, FDA and industry agreed to direct user fees toward certain post-market safety activities including acquisition of population-based data bases and validation of pharmacoepidemiological best practices.

If the Sentinel Network is established under the auspices of the Reagan-Udall Foundation, the Foundation may also raise private sector funding for the project. Under FDAAA, Reagan-Udall is authorized to "solicit and accept on behalf of the Foundation, any funds, gifts, grants, devises, or bequests of real or personal property made to the Foundation, including from private entities, for the purposes of carrying out the duties of the Foundation...." (21 USC § 379dd(i)). We expect that some private sector entities, non-profits, and non-governmental organizations would contribute to the Sentinel Initiative through the Reagan-Udall Foundation, provided that the goals of Sentinel are clear, the methods used meet those goals, and that the governance is robust.

III. PILOTING SENTINEL NETWORK VERSION 1.0:

The FDAAA legislation also establishes a timeline for implementing an active postmarket risk identification and analysis system, which requires FDA to "develop validated methods for the establishment of a postmarket risk identification and analysis

system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012;" (21 USC 351(k)(3)(ii))

This provision provides FDA with two reasonable approaches for meeting the requirement of a "Sentinel Network Version 1.0" by 2010.

1. Under the first option, FDA could establish a pilot system utilizing a single database of at least 25 million patients with the understanding that the underlying technological infrastructure would be temporary. During this pilot phase, the system and methods could be tested and lessons learned, before a new, comprehensive system including databases of at least 100 million patients is built from the ground up by 2012.

2. Under the second option, FDA could begin building a comprehensive, multi-database system to meet the 2010 deadline of 25 million patients. This system would be scalable and could be expanded over time using the same data standards and initial technological infrastructure to meet the 2012 deadline of 100 million patients.

BIO encourages the FDA to adopt the first approach, which would pilot the system to validate key methods and technologies and then build Sentinel Version 2.0 from the ground-up with new technological infrastructure. As lessons are learned, FDA and contractors may be forced to adapt or abandon certain technologies or standards. A pilot phase with temporary infrastructure would allow FDA to make these hardware changes without becoming burdened with legacy infrastructure that may be scalable, but fraught with unforeseen, built-in limitations.

Under the standards set forth in FDAAA, the Sentinel Network is intended to "identify" and "analyze" risks. However, there is still some public uncertainty regarding the fundamental function of the system. Before the pilot program is implemented, it will be important to clearly articulate in pilot program's operational policies whether the system will be used for signal detection and hypothesis generation, or signal confirmation and hypothesis testing, (or something in between such as "hypothesis strengthening.") BIO recommends that that pilot initially focus on signal confirmation, rather than signal detection. From technical standpoint, we believe that the methodologies around signal confirmation or hypothesis strengthening may be much more feasible to implement in the near term. After these approaches have been validated, additional attention should be turned to signal detection.

Finally, BIO encourages the FDA to publicly release the results of the pilot study. By doing so, FDA will help to build public support for future changes to the Sentinel Network policies and infrastructure, and disseminate important lessons learned to stakeholders.

IV. EPIDEMIOLOGICAL RESEARCH METHODOLOGIES:

The development of robust methodological approaches is a fundamental cornerstone of the Sentinel Initiative. We are pleased that FDA is assuming a leadership role to gather insights and pharmacoepidemiological best practices from industry, professional societies, academia, and other relevant stakeholders and we would like to offer the following recommendations:

- *Gap Analysis of Ongoing Pilots and Research Initiatives*: The Sentinel Network should be informed by the many ongoing initiatives in this area, such as FDA's contracted projects and pilot programs including the Observational Medical Outcomes Pilot (OMOP). As new knowledge and best practices are developed, FDA is well positioned to serve as central clearinghouse to disseminate those results. The appendix to FDA's 2007 Sentinel Initiative White Paper, which listed many of these ongoing research initiatives related to risk identification, assessment, and mitigation, was a useful resource for stakeholders. We believe that it would be helpful to build upon that list by conducting a gap analysis that can link the research purpose and timetables of the most relevant projects to specific project requirements necessary to successfully implement the Sentinel Network. Additionally, it would be helpful if FDA were to develop a compilation of major issues that need resolution, and a timeline that targets when each of these will be resolved - - in short, a publicly available work plan so that the work will progress at a reasonable pace and that internal and external research collaborations can be coordinated in a timely and effective manner.

- *Database Validation*: BIO agrees that there is not going to be one single data environment (i.e. database) that can answer all pertinent Sentinel Network research questions. For example, Medicare Part D data would not be an appropriate data source to study products indicated for pediatric populations. This is particularly true for biologics, which are often administered in specialty settings, and may require unique data sources to study potential safety signals. What is just as important as building a system of adequate statistical power, is establishing a system that correctly takes into account the unique attributes of the various data sources. During the pilot phase and initial implementation, FDA should establish a standard *validation process* for entering a single data environment to certify the quality and consistency of the data, and validate study methods for that particular database before using it to study actual safety signals. That general validation process can then be introduced to other data environments to expand the overall system.

- *Query Protocols*: BIO strongly believes that the queries and analyses of the Sentinel Network should be *protocol driven*, *prospectively designed*, and *publicly transparent*. In addition to detailing what epidemiological practices are *not* appropriate for studies using large databases, it may be helpful for FDA through guidance or public meetings to establish certain high-level guidelines or parameters around potential study protocols. To study common outcomes of interest, FDA and researchers could establish a number of standardized protocols based upon validated algorithms. Such established protocols would be helpful to

FDA, industry, and academics for understanding the strengths and limitations of queries of databases or particular indications. When developing protocols to query a Sentinel Network database, we also encourage FDA epidemiological staff to coordinate with the clinical staff to ensure that the results of the study are clinically meaningful.

- *Standardized Terminology:* Standardized terminology will also play an important role in the success of the Sentinel Initiative. We suggest that a standard coding dictionary should be adopted for all academics, government and industry use to allow for standard case definitions for Adverse Event terms and for disease definitions. For example, the SNOMED and MedDRA terminology sets are commonly used for these purposes depending on the relevant data environment. These standard case definitions should be adopted based upon rigorous methods and reviews including validation if possible to determine the reliability of the case definition.

- *Quality Assurance*: We also note that quality assurance -- the practice of checking that the cohort was correctly loaded from the database and that the programming matches the analysis plans -- is a critical element of any Sentinel Network research methodology. We propose the following terms be used to describe the three points of cohort creation that require quality assurances: data loading, programming for cohort assembly, and epidemiology analysis within the created cohort. We advise checking of programs by a separate programmer(s) to ascertain that the cohort was correctly pulled from the database, including a check against established reference counts provided by the database vendor prior to actually pulling the data, to ensure the appropriateness of the data loads. Epidemiologic analyses done within these created datasets will also need to be checked by separate epidemiologists to provide assurance that the analysis plans have been properly executed.

V. SIGNAL CONFIRMATION AND DATA ACCESS:

Before the first database analysis is conducted, BIO encourages FDA to decide how the accuracy and reliability of the results of that analysis will be confirmed or rejected. Elementary statistics dictates that some of the database searches will be false positives. How will FDA know the difference? If a signal is detected, what studies, of what design, on what databases, will be needed to confirm the signal? This all needs to be thought about and articulated before there are further efforts to find signals.

FDA should also spell out the roles that will be played by FDA, relevant sponsors, and the entity that did the database review. Confirmation of signals will likely require coordination between FDA and the drug sponsor, who has extensive first-hand knowledge of the product, because confirmation may require additional data analysis, and in some instances, post-market studies or trials. Therefore, we recommend that FDA notify relevant sponsors when a safety signal has been detected and additional confirmation may be necessary.

It will be important that sponsors have access to the research data in some form so that they can fully understand the scientific context of the safety signal, and further evaluate it, if necessary. Whenever a new safety risk is identified for a medical product or products, the Sentinel Initiative should allow for the relevant sponsors to have full access to the data in order to review the data analyzed and the methods used for the analysis. Otherwise, the sponsors will have no ability to ascertain whether the conclusions reached are correct, or determine if the research was inappropriately conceived or conducted. We recommend that the need for additional confirmatory research, including the sponsor's review of the data and the analyses, should be incorporated into the initial database contract to minimize the need for additional fees and secondary contracts for follow-up.

We also recommend that, where appropriate and consistent with applicable privacy laws, the data used for the Sentinel System should permit individual patient chart review. Otherwise, there will not be an ability to find out what confounding factors may have contributed to an adverse event. When FDA sees a signal, the Agency often insists that the sponsors provide data down to the individual chart level in order to understand the signal. We recommend that the Sentinel Network have that same level of completeness.

BIO also suggests that the FDA examine what constitutes the burden of evidence in observational research using electronic healthcare databases. In other words, when does FDA or a sponsor have enough confidence in a finding generated through observational research to warrant additional follow-up or regulatory action? For product approval, the standard for demonstration of efficacy is two well-controlled clinical studies, but the standard for safety findings in observational studies is yet to be defined. For example, would an observational study be confirmed if the findings are replicated: 1) in multiple databases using the same definitions, or 2) utilizing different methods or internal validation (i.e., randomly selected validation cohorts) in the same database? How would conflicting results be regarded, within or between databases? We suggest that FDA consider the variables, or axes of information, necessary to validate an observational study, including whether the analysis relied upon multiple methods, multiple databases, and/or multiple definitions over time.

It is important that FDA move proactively on identifying the burden of evidence, particularly as related to the following discussion on Benefit/Risk Communication. In light of the emerging broad availability of large-scale population-based databases such as Medicare Part-D, individual academic researchers may begin to publish analyses before the Sentinel Imitative has completed its efforts around pharmacoepidemiological best practices and validated study protocols. An existing evidence hierarchy will help put such publications into context and could shunt potentially counterproductive sensationalism.

VI. BENEFIT / RISK COMMUNICATION:

Ultimately, the Sentinel Network will serve little purpose if emerging product information is not appropriately communicated to the public in a clear and consistent manner within the context of the product's benefit/risk profile. Fully articulated benefit/risk communication policies and practices should complement an operational

Sentinel Network to provide patients and physicians with timely, accurate, and relevant information about the benefits and risks of a drug or biologic and how to manage newly emergent risks. However, to inundate the public with possible safety signals without proper context and regulatory oversight would undermine public confidence in the FDA and appropriate use of necessary medical therapies. It is important to balance public health and transparency with the potential for undue public concern that is not commensurate with the strength of the data, which may cause patients to abandon needed therapies without consulting a physician.

Therefore, we suggest that FDA develop a framework - or Good Benefit/ Risk Communications Practices - to articulate how and when Sentinel Network results are communicated. These Good Risk Communication Practices should articulate clear expectations, defined practices, and established timelines for FDA communication of new safety information. This framework should serve as a resource to FDA, sponsors, media, and the general public alike and should further define the responsibilities of each of the stakeholders that play a role in communicating benefit/risk information to the public.

For example, we recommend that drug sponsor should be informed of the results of such an evaluation well in advance of any external FDA communication so that the company may develop a complementary communications to the public and healthcare providers, or work collaboratively with FDA to establish a joint communication plan. This type of coordination between FDA and sponsors will help to minimize the potential for conflicting information and provide multiple channels of communication to better inform patients and physicians.

This framework should not only address what audience to communicate with and what medium to use to disseminate a message, but what risk information is appropriate to communicate. FDA should decide in advance what criteria will be used to decide if risks will or will not publicly communicated, because certain risks may be so infrequent or minor as to be clinically irrelevant or can be mitigated through other means. If FDA were to constantly communicate risks of minor, self-limiting or other insignificant risks to the public health, the public will not pay attention to and act upon important risks.

Another important consideration is at what time during the ongoing data analysis it is appropriate to communicate. BIO and its members think that the Sentinel Network must be designed so that the first communication of a new signal is accompanied by an analysis of the signal, and when appropriate, and a sensible recommendation to patients and physicians on next steps. In other words, FDA should not design nor permit the use of a system that would authorize the communication of risks of unknown validity with the actual meaning – and important information on how patients should be managed – coming months or years later. Rather FDA should design the system so that signal identification is immediately and robustly followed by confirmatory analyses – using either the same or different databases in a pre-designed manner.

Finally, in addition to addressing practices for communicating findings that confirm a safety signal, the framework should articulate a process for communicating findings that negate a previously communicated safety finding.

VII. CONCLUSION:

BIO appreciates this opportunity to comment on *The Sentinel Initiative: Structure, Function, Scope.* 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 (BIO)