July 2nd, 2004

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

Re: Docket No. 2004D-0189, 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 BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Draft Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

General Comments

The draft Guidance represents a substantive refinement of the concept paper upon which it is based and reflects FDA's thoughtful consideration of public commentary. In general, the document provides sufficient guidance to support initial implementation of its central concepts under most circumstances.

Particularly noteworthy in this draft Guidance is the consensus that routine pharmacovigilance suffices for most products and FDA efforts to ensure harmonization with international standards.

In keeping with the collaborative tone of the draft Guidance, BIO herein provides specific suggestions to assist in further refining the draft Guidance prior to finalization.

Specific Comments

Lines 97-99: "When planning risk assessment and risk minimization activities, sponsors should consider stakeholder input (e.g., from consumers, pharmacists, physicians, third party payers)."

Proposal: BIO requests clarification regarding the framework for identifying and obtaining input from stakeholders when planning risk assessment and risk minimization activities.

Lines 115-166, III. and IV:

Proposal: In keeping with FDA's efforts to achieve standardization, BIO recommends using an internationally accepted definition of pharmacovigilance, such as that proposed by WHO and referred to in the International Conference on Harmonisation (ICH) E2E guideline:

> The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (*Source: The Importance of Pharmacovigilance, WHO 2002)*

Lines 121-123, 125-127, 361-384, and 327:

Comment: Although the draft Guidance gives several approaches to signal detection, the term "signal" has not been defined.

Proposal: Effective communication and decision making about risk requires a clear definition of "signal". BIO recommends that FDA base the definition on a unifying concept that supports multiple approaches to signaling. To this end, BIO suggests that FDA adopt an existing definition such as that proposed by WHO:

> Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. (Edwards IR, Biriell C. Drug Safety 1994; 10: 93- 102)

The draft is much improved in terms of guidance concerning signal detection. However, we believe it misses an opportunity to provide general guidance concerning key aspects of signal evaluation. To this end, BIO suggests that FDA explicitly address the manner in which the quality of information (i.e., level of evidence) influences signal interpretation. For example, we suggest including a statement to the effect that, in general, the more reliable the source, the more well established the diagnosis and the more rigorous the conditions under which the data were gathered, the more likely a

signal is to represent a risk. As a corollary, FDA might add that caution should be exercised against over-interpreting a potential signal that is based on poor quality information and that cannot be confirmed by a certified medical professional.

Lines 155-157: "FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors."

Comment: BIO strongly agrees with the risk-based (i.e., seriousness of the reported event) and information-based (i.e., report' s origin) approach to establishing the intensity of follow-up.

Lines 259-268: "FDA does not recommend any specific categorization of causality, but the categories *probable, possible,* or *unlikely* have been used. The World Health Organization uses the following categories:[1]"

- certain;
- probably/likely;
- possible;
- unlikely;
- conditional/unclassified; and
- unassessable/unclassifiable.

Comment: We believe any causality scale should allow for the possibility that an event is *not related* to product; e.g., an event with onset before initiation of product that does not worsen after product initiation.

Lines 316-317: "Data mining is not the only technique used to make causal attributions between products and adverse events."

Comment: The sentence concerning data mining suggests that data mining is considered a tool for causality assessment. BIO feels strongly that data mining, particularly when applied to unstructured data (e.g., spontaneous reports) is best thought of as merely hypothesis generating.

Lines 325-327: "The statistic (or score) used to quantify the disproportionality between the observed and expected values for a given product-event combination is compared to a threshold that is chosen by the analyst to optimize sensitivity and specificity."

and 347-350: "FDA recommends considering signals identified by scores that exceed a specified threshold as hypothesis-generating. Further investigation of a product-event combination may be warranted, especially if the event is serious and unlabeled or raises other safety concerns as described in section IV.F."

Comment: Given the low positive predictive value of data mining of unstructured data (e.g., spontaneous reports), and given that the work required for signal evaluation is orders of magnitude

[1] World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Products*.

greater than that required for detection, pharmacovigilance systems would be overwhelmed if every event that exceeded a data mining threshold required in-depth evaluation. Therefore, BIO strongly agrees with the FDA's position that merely exceeding a numeric data mining threshold does not automatically require in-depth evaluation of the event in question. As implied by the draft, the threshold for further evaluation should, in addition, take into account the sensitivity of the criterion (false positive rate) as well as the medical, pharmacoepidemiologic and regulatory nature of the event and the severity of its consequences.

Lines 410-412: "FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.[2]"

Comment: BIO is concerned that the draft restricts the calculation of reporting rates to United States data only.

Proposal: We strongly suggest that FDA allow for inclusion of global data in the calculation of reporting rates for purposes of signaling.

Lines 417-418: "Comparisons of reporting rates can be valuable, particularly across similar products or across different product classes prescribed for the same indication."

Comment: The draft appropriately addresses the importance of disease/indication in signaling. However, it does not address comparisons of similar products used for different indications.

Proposal: BIO suggests the addition of a caution in comparing similar products that are used for different indications particularly when there is disparity in the co-morbities, therapeutic regimens and clinical consequences of the diseases in question.

Lines 489-493: "Because pharmacoepidemiologic safety studies are observational in nature, they are more subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. This problem can usually be surmounted when the relative risk of exposed patients is high or the study is sufficiently large to detect small differences in relative risk."

Comment: BIO agrees that large relative risks are not likely to be produced by confounding. As such, large relative risks that are estimated with a high level of precision warrant careful consideration, even when unadjusted, as potential risks. However, BIO strongly disagrees with the suggestion that bias can "usually" be overcome by increases in sample size. A large sample will only provide a more precise estimate of the bias in a biased analysis. On the other hand, a large sample size may permit adjustment for properly characterized confounders and, thereby, support more reliable inferences about event-product combinations, to the extent that the adjustment technique is justifiable.

[2] See Rodriguez EM, Staffa JA, Graham DJ, (2001), *The role of databases in drug postmarketing surveillance*, Pharmacoepidemiology and Drug Safety, 10:407-10.

Lines 564-569: "The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."[3]

Comment: BIO commends FDA for providing clear definition of the term "registry", as it applies to the Guidance.

Lines 638-639: "To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates."

Comment: BIO disagrees that data mining, particularly of unstructured data, can be used to further characterize safety signals to determine if they represent risks. BIO agrees with FDA's position stipulated earlier in the document that data mining is best considered a tool that supports hypothesis generation. However, we do not believe data mining of unstructured data is a tool for establishing that a product causes an event.

Lines 692-694: "As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously."

Comment: BIO emphasizes the importance of benefit-risk balance in the risk management equation.

Proposal: BIO suggests that the benefit side of the equation be given more emphasis earlier in the Guidance and underscores the fact that the science and methodology of benefit-risk, as it applies to the pharmaceutical industry, is evolving.

In conclusion, we appreciate the opportunity to provide our comments and look forward to finalization of the Guidance.

Sincerely,

Sara Radcliffe
Director
Science Policy and Bioethics

[3] See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at http://www.ncvhs.hhs.gov.