July 2nd, 2004

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

Re: Docket No. 2004D-0187, 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 BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Draft Guidance for Industry: Premarketing Risk Assessment.

General Comments

Three draft Guidances have been published by FDA on risk management activities:

- Pre-marketing Risk Assessment
- Development and Use of Risk Minimization Action Plans (RiskMAPs)
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

These draft Guidance documents are intended to encourage evidence-based risk assessment for all products in development and for marketed products. However, these guidelines may require the sponsor to undertake substantial activities beyond existing regulatory requirements. Thus, BIO

believes it is important to evaluate the utility of each proposed measure of risk assessment to ensure that it can appropriately identify or exclude the risk of interest. We also believe any risk assessment plan must be feasible. Similarly, risk minimization plans should be aimed at achieving a specific target reduction of risk that is meaningful to the well being of the population at risk. Efforts to assess and minimize risk must be proportional to the gains. These comments apply to both pre-marketing risk assessment and post-marketing efforts.

BIO is pleased to note that many of our comments on the FDA Concept Paper on Pre-Marketing Risk Assessment of May 2003 are reflected in the Draft Guidance. In particular we welcome the reaffirmation (lines 127-128) that "Providing detailed guidance on what constitutes an adequate safety database for all products is impossible", and that references to an "ideal" safety database have been removed. In that spirit, the concept of "appropriate" has replaced the notion of "ideal" in describing the characteristics of a safety database. By making this explicit, the applicability of the guidance is strengthened. BIO believes that the affirmation that risk assessment efforts must be tailored to the specific product, indication and safety concern is critical to addressing these issues.

Specific Comments

Lines 76-77: "To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate."

Comment: We believe this statement is inconsistent with the reality that these guidelines are not in harmony with the emerging international proposals on definitions and standards. In this document, FDA's proposals differ from those included in the ICH E2E Pharmacovigilance Planning Step 2 document and therefore, may result in requirements and definitions in the United States that differ in fundamental ways from those of ICH E2E. This will affect data analysis and presentations as well as the structure of documents. Risk assessment and minimization plans may need to be implemented internationally and these differences will confound such efforts. Although this draft Guidance affirms the need for harmonization, we find that the steps to implement such proposals are not clearly defined in the document.

Proposal: BIO recommends that the draft Guidance not be finalized until the relation to ICH E2E is clarified and suggest that the final Guidance ensure that requirements in risk assessment and management are harmonized. We believe conflicting and competing concepts and strategies for managing risk are inefficient and also inconsistent with the goal of optimizing patient safety.

Lines 262-265: "Generally, serious events that rarely occur spontaneously (e.g. severe hepatocellular injury or aplastic anemia) are of significance and interpretable whenever they occur since the expected rate is essentially zero in populations of any feasible size. They thus can usually be appropriately interpreted without a control group."

Comment: This statement assumes that the cases of such rare events are 1) well documented and 2) there is no alternative explanation for the event. One example would be if a patient is reported to have aplastic anemia but has a hemoglobin of 10 grams and abundant reticulocytes. Such a case should not be interpreted as a valid report of this rare condition. On the other hand, a patient with a confirmed

diagnosis of aplastic anemia who has documented, recent benzene exposure would not necessarily be considered "interpretable".

Proposal: We recommend adding the qualifiers "well documented" and "without a plausible alternative explanation" to this statement:

> "Generally, **well documented**, serious events, **without a plausible alternative explanation**, that rarely occur spontaneously (e.g. sever hepatocellular injury or aplastic anemia) are of significance and interpretable whenever they occur since the expected rate is essentially zero in populations of any feasible size. Thus, they can usually be appropriately interpreted without a control group."

Lines 279-292, IV. B. 2: *A Diverse Safety Database*

Comment: Throughout the three draft Guidance documents, the importance of evidence-based approaches and the use of validated methods are emphasized. We believe that these same principles should apply when designing pre-marketing risk assessment strategies. Whenever a tool for improved risk assessment is employed there should be good reason to believe that it will provide relevant, interpretable and pertinent information. We believe focused, differentiated approaches to risk assessment should be designed to delineate the risks of interest for the specific product and indication under development. For this reason we continue to have concerns about the notion of a "diverse safety database" in a Guidance regarding premarketing risk assessment.

Although a diverse safety database is indeed likely to be more representative and more readily generalizable to the post-marketing population, it must be derived from premarketing studies and will thus influence their design. As a result generating a diverse safety database has substantial implications for product development. Inclusion of a more diverse population in pivotal studies makes it more difficult to demonstrate efficacy; such groups have more confounding factors such as concomitant diseases and medications. They may also be less compliant, leading to more study dropouts and missing data. The consequence of each of these factors is to increase the number of patients in order to demonstrate efficacy, or its absence.

Furthermore, the resulting more "diverse" safety database may not always provide a better basis for assessing risks in the expanded population. The numbers of patients in each sub-group in the diverse population may well be too small to assess sub-group specific risks. Indeed, the risks detected would have to be high for them to be measurable in the premarketing setting. A further potential hazard to this approach is that the heterogeneous population might generate so much "noise" that real safety signals could be obscured. Thus while a diverse safety database may be desirable, we believe it should not be a premarketing requirement. In addition, many of the issues of safety in populations not adequately studied in phase III are best addressed by other means.

There are several practical issues related to obtaining a diverse safety database:

- Such a diverse safety database will have to significantly increase the size of the safety database, which will require a longer drug development period,
- sub-analyses based upon a diverse safety database may not be conclusive due to small sample sizes for each subgroup, and
- there will be a dilution of the focus of the clinical development program.

Proposal: Consequently, BIO recommends that the potential benefits be weighed against the resultant impacts on a case-by-case basis.

Lines 294-318, IV. B. 3: *Exploring Dose Effects Throughout the Clinical Program*

Comment: A major benefit of multiple doses is not only to evaluate the risks but also the benefits at different dose levels.

Proposal: Should various doses be considered, we recommend that evaluation consider both benefit and risk.

Line 325 (and throughout the guidance):

Proposal: BIO believes it is necessary to clearly define and use the terms "efficacy" (controlled environment) and "effectiveness" (real life, non-controlled environment).

Lines 382-386: "A comparative study could show whether the toxicity profile for the established therapy is generally similar to that for the novel therapy, or whether important differences exist."

Comment: We believe there are practical issues with this text in that obtaining comparative data in addition to demonstrating that a candidate is safe, efficacious and of high quality would delay development timeframes due to the need for additional patients. This requirement also implicitly alters the standards for approval.

Lines 406-471, V. A: *Risk Assessment During Product Development*

Comment: Many of the strategies recommended in this section, for example large simple safety studies, assume the presence of a large patient population. However, these approaches are inherently inappropriate for rare diseases. We believe additional thought should be given to techniques appropriate to assess risk for orphan diseases and ultra-orphan diseases. This is especially important for the future since pharmacogenomics and other molecular biologic insights are likely to define smaller, more homogeneous "disease entities" which are the target of highly specific therapies. In such settings, benefit relationships change since a higher proportion of the treated patients are likely to be responders.

Proposal: BIO believes it may be appropriate to explore the assessment of risk in small patient populations in a separate forum.

Line 417: "…titration on safety (and efficacy)."

Proposal: We recommend omitting the parentheses, i.e., would read… "safety and efficacy."

Line 443: "In some circumstances, a large, simple, safety study (LSSS) may be appropriate."

Comment: BIO believes there are numerous challenges with conducting a LSSS prior to registration. In addition, clarification is needed regarding when a LSSS should be conducted. Such a study could substantially lengthen development timeframes without positively altering the benefit risk relationships. In addition, for many rare events, LSSS may not provide sufficient power to determine the risk.

Proposal: We recommend that the potential benefits be weighed against the resultant impact on a case-by-case basis.

Line 519, V. C: *Safety Aspects that Should Be Addressed during Product Development*

Comment: BIO appreciates the clarification that requirements to evaluate certain toxicities (lines 524-529) are for "small molecule development programs".

Lines 557- 559: "We recommend that sponsors address the unique safety concerns pertaining to the development of any particular biological product with the relevant product office."

Comment: BIO appreciates the emphasis on collaboration and product-specific approaches to safety issues related to biological products.

Lines 872-881, IV. G: *Long-term follow-up*

Comment: Clarification is needed regarding what constitutes "long-term follow-up". In this discussion it appears to describe follow-up for patients who drop out of the study. The term "long-term follow-up" is also being used to describe a recommended program of 15 years of follow-up for gene therapy products.

Proposal: We recommend that the phrase "long-term follow-up" not be used without clarification.

In conclusion, BIO looks forward to final guidance from FDA on risk assessment based on a paradigm emphasizing evidence-based strategies and the development of approaches that are crafted to the unique situation that each product development undertaking represents. This approach will help ensure that innovative, effective and safe biologic products continue to be developed to meet serious unmet medical needs.

Sincerely,

Sara Radcliffe
Director
Science Policy and Bioethics