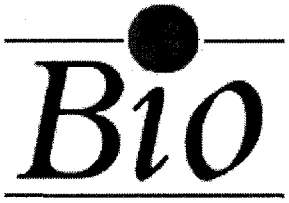

BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

May 19, 2004

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

Re: Docket No. 2004D-0117, Federal Register: March 30, 2004 (Volume 69, Number 61, Page 16579-16580)

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 45 U.S. states and 32 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 on ICH E2E: Pharmacovigilance Planning (PvP) Draft Version 4.1 dated on 11th November 2003.

BIO appreciates the efforts of the International Conference on Harmonization to facilitate product development, review, approval, and post-market monitoring on an international basis. We believe these efforts advance the goals, shared by the participating countries and product sponsors, to improve timely access by patients to products that are safe and effective and by the health care system to information about approved products that emerges after the products are in the marketplace.

In general, we believe the guideline reflects those goals and will provide a useful framework and set of parameters for product sponsors. We have only a few comments, organized below according to the document's headings and subheadings.

Background and Scope

One significant concern is that the document appears to treat the pharmacovigilance plan not as a dynamic program but as a snapshot of the situation at the time of regulatory submission. BIO believes that the process of identifying and evaluating risks is an ongoing one that starts before product approval and extends throughout the life cycle of the product. Development of a plan for monitoring and controlling risks likewise must be dynamic, with plan implementation subject to modification as needed. BIO urges that this concept be presented more clearly and strengthened in this document and that the view of both the pharmacovigilance specification and the pharmacovigilance plan as on-going dynamic documents be reinforced.

BIO believes that the scope of the guidance should not be limited to marketed products. Many of the principles laid out in the guideline are appropriate for pre-market risk assessment and the process of developing pharmacovigilance specifications and a pharmacovigilance plan begin in the pre-market phase. Both the plan and the specifications evolve in the course of clinical development and beyond, into the post-market phase. These documents may become part of the regulatory submission.

We suggest adding these concepts into the document by noting specifically the applicability of the principles to pre-market risk assessment; that the specifications and plan can be prepared and updated at various points in the course of product development as well as at the time of approval; and that the principles may be adapted to safety surveillance during product development, as appropriate.

We also recommend that the pharmacovigilance plan always be a separate, stand-alone document, not a part of the Common Technical Document (CTD). Since elements of the plan will be region-specific, we believe its inclusion in the CTD could undermine the utility of that document as a single structure for all regions. While the pharmacovigilance plan and specifications should be correlated with the CTD, there is currently no agreement among regions about whether they should be part of it. BIO believes this lack of agreement is another reason not to incorporate all the documents into one.

Pharmacovigilance Specification

The document notes that the specification summarizes both identified and unidentified risks. We believe "unidentified risks" should be more narrowly defined and limited to directly relevant situations for which specific actions are planned. We suggest modifying the requirement that the specification summarize identified and unidentified risks, populations at risk, and situations not adequately studied by adding the limitation where the drug product is likely to be used and by stating that the pharmacovigilance specification can be built initially during the pre-marketing phase and at the time approval is sought it would reflect the status of issues that were being followed during development.

As currently drafted, the guideline states that information in the CTD should serve as the basis for the safety issues identified in the pharmacovigilance specification. BIO believes that while the safety overview, conclusions regarding benefits and risks, and safety summary sections of the CTD may correspond with the specifications, one does not necessarily directly follow the other. The CTD does not link the safety problems that were being followed in the course of product development and the recommendations made in the Overview of Safety and Summary of Clinical Safety, and provides no opportunity for issue-based assessment. The CTD safety sections provide for structured information, not a full discussion of the problem and how it has been or is being addressed. We believe this issue-based assessment is the kind of information that should be included in the pharmacovigilance specification and why the document should be separate from the CTD. This would allow for integrating information in a problem-oriented fashion. Rather than recapitulating information from the CTD, we recommend the pharmacovigilance specification focus on the open issues for which a plan is needed. For each issue, we suggest there be a summary of the relevant information, followed by an assessment and an identification of the pharmacovigilance plan element that applies to that issue.

Limitation of the human safety database

The guideline anticipates discussion, in the pharmacovigilance specification, of "any regulatory actions related to safety." BIO agrees that this discussion should take place and recommends that sponsors be encouraged to discuss specific ongoing safety issues on an issue-by-issue basis, including both preclinical and clinical data that are pertinent to the problem.

Adverse events

BIO recommends adding explanatory language noting that the discussion of risk factors and potential mechanisms should draw on information from any part of the CTD (preclinical and clinical) and other relevant information such as other drug labels, scientific literature, and post-marketing experience. Similarly, we believe the guideline should state that discussion of potential risks also can draw on or be based on information from any part of the CTD. Further, we recommend data from epidemiologic studies and relevant information from pharmacological class effects be incorporated into these risk discussions.

Pharmacovigilance Plan

BIO believes that the pharmacovigilance plan should not only be based on the specification, but should correlate with it on a problem-by-problem basis; we recommend the guideline reflect this.

Structure of the Pharmacovigilance Plan

In summarizing the ongoing safety issues, BIO recommends that the plan include only those important identified risks that require additional characterization and for which a plan will be undertaken. We believe the guideline should specify that the "important missing information" is information that will need to be collected in implementing the plan. BIO suggests that the pharmacovigilance plan be integrated with the specific problems addressed. It may be that a single instrument such as an epidemiological study or a registry will produce information relating to several problems; we believe that should be outlined and discussed when the specific study proposal is presented.

Conclusion:

In conclusion, BIO believes this document, with a few relatively minor changes, will be very helpful as product sponsors analyze the risk-benefit calculus for their products and take steps to address risks both during product development and after marketing. We recommend that the guideline present more clearly and forcefully the notion that pharmacovigilance is not a one-time event, but a process that begins early in development and lasts through the life of the marketed product. It is a process that recognizes and allows for change as populations and product uses change, and as more information is obtained. We believe the dynamic nature of pharmacovigilance needs to be emphasized.

We further emphasize the importance to product sponsors of FDA's acceptance of ICH standards, to achieve true international harmonization. BIO remains concerned that FDA not treat ICH guidelines as a "floor" on which further FDA regulatory requirements expand. In the pharmacovigilance area, as in others, BIO urges FDA to coordinate its guidance with that of ICH, perhaps issuing separate FDA guidance only in those cases where U.S. requirements are necessarily different from those established by the ICH.

Thank you for the opportunity to comment on this document. If there is any way we may be of further assistance as this guideline, the FDA guidance, or other proposals in this area move forward, please do not hesitate to contact us.

Sincerely,

Sara Radcliffe

Sara Radcliffe
Director
Science Policy and Bioethics