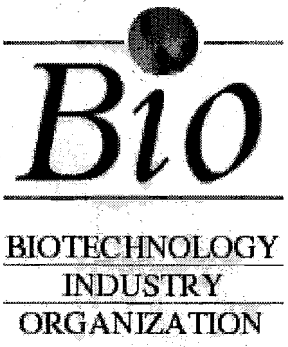

January 13, 2006

CAPT Michael Carome, M.D.
U.S. Public Health Service
Associate Director for Regulatory Affairs
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Request for Public Comment on OHRP's Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (DRAFT – October 11, 2005)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comments on the Office for Human Research Protections' (OHRP's) *Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others*. 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. The BIO Safety Reporting Group, which is composed of pharmacovigilance specialists, developed the comments and recommendations conveyed in this document.

General Comments

BIO strongly supports ongoing efforts, such as those by the Federal Adverse Event Task Force, to improve adverse event (AE) data collection in clinical trials, reduce the soaring volume of individual case safety reports (ICSRs) that sponsors and clinical investigators file with institutional review boards (IRBs) and independent ethics committees (IECs), and harmonize adverse event reporting

requirements. Comprehensive solutions are needed to address the gaps and problems within the adverse reporting system that regularly confound the research community.

We agree that the current practice of sending large numbers of ICSRs to IRBs/IECs is burdensome, inefficient, and fails to provide investigators and IRBs/IECs the information they need to make informed benefit-risk decisions to fully protect the rights and welfare of human study subjects. Ambiguity and inconsistencies in global safety reporting regulations have contributed to this problem. When there is regulatory uncertainty, sponsors often default to the lowest common global denominator and send more than is necessary.

BIO endorses most of the concepts and principles in the OHRP *Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others*, which are intended to channel meaningful safety information to IRBs/IECs during human research conducted or supported by the Department of Health and Human Services (HHS). Unfortunately, current sponsor practices work against many of the concepts and principles proposed in the OHRP draft guidance, because safety reporting regulations that drive sponsor behavior are not yet aligned.

We agree it makes sense to minimize the burden on IRBs/IECs by implementing new policies and procedures that more effectively and efficiently provide IRBs/IECs the information they need to perform evidence-based benefit-risk assessments. Although not the ultimate solution, we think it is reasonable for IRB/IECs to set up triage systems that allow external and internal adverse events (as defined in the OHRP draft guidance) to be processed differently in accordance with policies and procedures established by and acceptable to the IRBs/IECs. Of course, eliminating the reason IRBs/IECs need to implement triage systems should be considered. The concept of third parties [e.g., sponsor, designated safety monitor, or data and safety monitoring board (DSMB)] analyzing aggregate safety data and providing investigators and IRBs/IECs a concise summary of the evolving safety profile of an investigational medicinal product rather than ICSRs makes the most sense.

To deal with the soaring volume of ICSRs they receive from investigators, who may be following protocol instructions to forward all safety reports they receive from the sponsor directly to their IRBs/IECs, many IRBs/IECs have already implemented triage policies and procedures similar to those proposed by OHRP to limit receipt of information they consider un-interpretable and/or of low value in the context of safety monitoring. Emergence of these new, but often variable IRB/IEC practices in the absence of supportive and harmonized regulatory guidance, raises potential good clinical practice (GCP) compliance questions.

For example, when sponsors monitor study site performance, what are the acceptable standards against which they should audit with respect to

investigators keeping IRBs/IECs adequately informed of emerging safety information? Is it more important for sponsors to assess if study sites and their IRBs/IECs have appropriate systems in place to appropriately receive and review safety information received from sponsors, or should the focus be on whether or not investigators forward ICSRs received from sponsors directly to their IRBs/IECs?

The relevant US regulation that frames investigator to IRB communication requirements (21 CFR §312.66) simply states that investigators should promptly report to the IRB all *unanticipated problems* involving risk to human subjects. What, how and when to report are not specifically addressed. Are the concepts and principles proposed in the OHRP draft guidance consistent with the intent and spirit of 21 CFR §312.66 and related international regulations? If the answer is yes, supporting and harmonized regulatory guidance needs to be developed.

Although the *Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others* conveys logical principles, clarifies the intent of current HHS OHRP regulations pertaining to safety reporting, and aims to reduce the volume of ICSRs received by IRBs/IECs, the guidance by itself will not address the root cause of why IRBs/IECs are being inundated with ICSRs from multiple sources. The root cause is inconsistent and conflicting regulations governing sponsor adverse event reporting obligations during clinical trials.

OHRP and the Food and Drug Administration (FDA) will need to issue harmonized joint guidance and update old regulations to effectively solve the problem of over reporting of ICSRs to investigators and IRBs/IECs and other problems within the adverse reporting system.

In addition to the problem of excessively large numbers of AEs being reported to IRBs/IECs, which is making it difficult to separate true safety signals from "noise," the lack of commonly applied AE definitions and good AE reporting principles in clinical trials is contributing to amorphous, imprecise and inconsistent safety data collection.

Thus, BIO strongly encourages OHRP, other HHS offices, and FDA to perform a thorough work flow analysis to identify comprehensive solutions that address common problems experienced by investigators, their IRBs/IECs, and sponsors, and that achieve the following objectives:

- Clarify and harmonize terms and definitions used by the various US regulatory agencies (e.g., "adverse event" or "unanticipated problem" vs. "unexpected") and align applicable safety reporting policies.
- Develop good AE reporting guidance to improve the quality, precision and consistency of AE reporting by investigators to sponsors;

- Clarify and harmonize requirements for expedited reporting of ICSRs from sponsors to investigators and/or IRBs/IECs;
- Clarify and harmonize requirements for expedited reporting of ICSRs from investigators to IRBs/IECs; and
- Identify and implement new best practices for analyzing and disseminating emerging safety information from ongoing clinical trials to regulators, investigators and IRBs/IECs, such as those proposed by the Council for International Organizations of Medical Sciences (CIOMS) VI Working Group.

More specific comments and recommendations pertaining to certain sections of the OHRP draft guidance as well as broader issues follow.

Comments/Recommendations Regarding OHRP Draft Guidance

I. What are adverse events?

Some of the term definitions in the OHRP draft guidance, or lack thereof, are inconsistent with those in applicable regulations/guidance that sponsors commonly apply in the context of safety reporting.

Noteworthy is that the OHRP draft guidance does not define or use the term *adverse event* and states there is no common definition of this term across government and non-government entities. OHRP considers adverse events to be defined in very broad terms and to include any event meeting the criteria for any of five different AE definitions summarized in Appendix A. This lack of clarity regarding the definition of an *adverse event* in US safety reporting regulations and guidance documents is problematic because use of consistent terminology is essential to good AE reporting and communication.

The draft guidance also indicates that OHRP considers the terms *expected* and *anticipated* (and the terms *unanticipated* and *unexpected*) to be synonymous, and defines an *expected adverse event* as an event previously known to or anticipated to result from:

a) the interventions and interactions used in the research;
b) the collection of identifiable private information under the research;
c) an underlying disease, disorder, or condition of the human subject; and/or
d) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

For purposes of safety reporting, sponsors commonly apply different definitions of *expected* and *unexpected* than OHRP. For example, the CIOMS V Working Group has published that the concept of expectedness "refers to events that may or may not have been previously observed and documented. It does not refer to

what might be anticipated (expected in a different sense) from the known pharmacological properties of a medicine, nor does it refer to what may occur in the course of the treated disease such as in the case of disease progression." In related commentary, CIOMS V explains that a reported AE should be classified as *unexpected* for regulatory reporting purposes, unless the event is mentioned in the appropriate reference safety information document(s) and positioned as at least possibly causally related to the medicinal product.

The CIOMS V concept of expectedness, which is the industry standard for purposes of safety reporting, conflicts with related concepts conveyed in the OHRP draft guidance. These inconsistencies in definitions will result in sponsors sending investigators ICSRs that they classify as *unexpected* for regulatory reporting purposes but that OHRP and IRBs/IECs might consider *expected*.

To promote consistency in AE reporting, BIO strongly recommends that OHRP, other HHS offices and the FDA incorporate common AE and related definitions into applicable safety reporting regulations and that supplementary guidance be developed to address common sources of AE definition confusion.

To align with international harmonization standards, it is recommended that a common AE definition be based on the International Conference on Harmonization (ICH) E2A guidance that defines an adverse event (or adverse experience) as:

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

In practice, the term "pharmaceutical product" in the above ICH E2A definition of an AE is commonly modified or broadened by sponsors to include a "medical device" and/or any "protocol-imposed intervention" as appropriate depending on the specifics of the independent research study. For example, some sponsors may define an AE as:

"Any unfavorable or unintended event associated with a research study."

Sponsors often incorporate additional AE reporting guidance in protocols to address issues that complicate the capture of meaningful AE data with respect to characterizing the true safety profile of an investigational product – such as how pre-existing medical conditions (including the disease under study) and associated manifestations should be handled during a clinical trial.

For example, the ICH E9 guideline (Statistical Principles for Clinical Trials) mentions that, when substantial background noise of signs and symptoms is anticipated in a clinical trial, one method to reduce such noise is to make use of the "treatment emergent" concept in which AEs are recorded only if they emerge or worsen relative to pre-treatment baseline. The application of the treatment emergent concept when substantial background noise of signs and symptoms is anticipated facilitates the capture of AEs that potentially could be related to study treatment and is probably the most appropriate capture definition for purposes of safety analyses.

Protocols that incorporate the treatment emergent concept into the ICH E2A definition of an AE might instruct investigators to report: (1) any unfavorable or unintended sign, symptom or disease that emerges during a study's defined active phase having been absent pre-study (i.e., anything new), regardless of attribution; or (2) any pre-existing medical condition that worsens in severity or frequency or that changes in nature during a study's defined active phase (i.e., any change), regardless of attribution.

Despite the aforementioned published ICH guidance, common AE definitions and practical AE reporting guidance have not been consistently and broadly incorporated into safety reporting regulations that shape industry practices.

To the extent possible, BIO recommends that OHRP, FDA, and other federal agencies harmonize regulations and guidance concerning adverse event reporting in clinical trials.

II. What are external adverse events versus internal adverse events?

The OHRP draft guidance defines *external adverse events* as ICSRs of AEs experienced by subjects enrolled in multi-center clinical trials that originate from sites other than the site(s) over which the IRB/IEC has jurisdiction. It also states that HHS regulations do not require sponsors to distribute external adverse event reports (which could include serious and unexpected adverse drug reactions from external sources) to all principle investigators (PIs) at all study sites. This OHRP guidance may conflict with US and ex-US safety reporting regulations that investigators and sponsors interpret as mandating broad distribution of *external adverse events.* The OHRP draft guidance defines *internal adverse events* as ICSRs of AEs experienced by subjects enrolled at the site(s) under the IRB's/IEC's jurisdiction for either multi-center or single-center research projects.

Although the distinction between external and internal AEs clarifies reporting requirements to local IRBs/IECs for clinical studies conducted or supported by HHS, these distinctions are not evident in FDA regulations that govern sponsor and investigator AE reporting obligations during clinical trials conducted under an investigational new drug (IND) application (i.e., 21 CFR §312.32, §312.64 and §312.66) or in equivalent ex-US safety reporting regulations. Many investigators

and sponsors conservatively, and perhaps incorrectly, interpret current regulations to require expedited reporting of all serious and unexpected adverse drug reactions (ADRs) from any source to the FDA, all investigators actively studying the molecule in clinical trials and their IRBs/IECs, and other regulatory and research agencies in the US and abroad.

While requirements for expedited safety reporting from sponsor to regulatory authorities are largely harmonized globally, similar requirements for reporting to investigators and IRBs/IECs are not. The ICH E6 guideline on GCP states that "the sponsor should expedite the reporting to all concerned investigator(s)/institution(s), the IRB(s)/IEC(s), where required, and to the regulatory authority (ies) of all ADRs that are both serious and unexpected." No distinction is made between external and internal AEs in the ICH E6 guidance.

The current US IND safety report regulation (21 CFR 312.32) requires sponsors to expeditiously inform all investigators conducting trials registered under the same IND of all events/information that qualify for expedited reporting per criteria set forth in the regulation. Following implementation of the ICH E6 guideline, other countries now require that the same reports that are expedited to regulatory authorities also be sent to investigators in all countries where clinical trials of the investigational product are being conducted.

The European Union (EU) Clinical Trial Directive introduced the term and acronym *Suspected Unexpected Serious Adverse Reaction* (SUSAR) in connection with expedited reporting requirements. The Directive states that all SUSARs which occur in a concerned trial are subject to expedited reporting from the sponsor to concerned competent authorities and to the IECs concerned. These would be considered *internal adverse events* as defined in the OHRP draft guidance. Additionally, for investigational medicinal products that have not a marketing authorization in any member state of the European Community, any other SUSARs associated with the investigational product from any source are also subject to expedited reporting. These could be *external adverse events* as defined in the OHRP draft guidance.

Unlike US IND safety reporting requirements, the EU Clinical Trial Directive does not include a requirement for routinely sending individual SUSARs to investigators. Instead, national authorities within the EU have the option to require sponsors to provide investigators periodic safety summaries, which BIO believes is a more effective and efficient method to convey important safety information.

International requirements for reporting safety information to IRBs/IECs are less well defined and equally inconsistent. As mentioned above, the ICH E6 guideline only specifies that reports be expedited to IRBs/IECs "where required." FDA regulations imply that IRBs/IECs can define what information they must receive from investigators. However, since sponsors are also responsible for ensuring

that investigators follow GCPs, including rules established by IRBs/IECs, many sponsors routinely instruct investigators to forward all expedited reports to their respective IRBs/IECs even though this may conflict with policies and procedures established by IRBs/IECs.

When faced with inconsistent regulatory reporting requirements, sponsors may often take the most inclusive approach and send everything to everyone. Lack of clear and consistent regulatory guidance is the root cause of investigators, and in turn their IRBs/IECs, receiving a staggering and ever increasing volume of ICSRs from sponsors, which they are ill equipped to manage and interpret.

This problem will likely continue until new regulatory guidance is issued that clarifies and harmonizes current practices and/or replaces routine expedited case reporting by sponsors to investigators and/or IRBs/IECs with periodic safety summaries based on sponsor and/or independent expert assessment of accumulating information in aggregate, such as those proposed by the CIOMS VI Working Group.

Rather than trying to establish separate and complex instructions for reporting potentially important external and internal adverse events to investigators and IRBs/IECs, BIO endorses the CIOMS VI Working Group proposal to eliminate routine expedited case reporting by sponsors to investigators and IRBs/IECs. Instead, CIOMS VI recommends that sponsors provide regular updates of the evolving benefit-risk profile of an investigational product that highlight important new safety information. Significant new information and occasionally a single case report that has implications for the conduct of the trial or warrants an immediate revision to the informed consent would be communicated on an expedited basis. More commonly, important new safety information would be communicated periodically, based on the assessment of accumulating information in aggregate.

BIO encourages the FDA and other regulatory agencies to consider the CIOMS VI Working Group proposal and to convene the appropriate stakeholders to develop agreed to standards for periodic safety updates.

III. What are unanticipated problems, and how do they relate to adverse events?

In our comments pertaining to question I., it was noted that sponsors may apply different definitions of *expected* and *unexpected (i.e., unanticipated)* than those conveyed in the OHRP draft guidance. These inconsistencies in definitions can result in sponsors sending investigators many ICSRs that they classify as *unexpected* for regulatory reporting purposes but that OHRP and IRBs/IECs would consider *expected*. BIO recommends that safety reporting definitions be harmonized across all US safety reporting regulations and guidance documents to eliminate this confusion.

The OHRP draft guidance states that the following three categories of adverse events should always be considered *unanticipated problems* and need to be reported under the HHS regulations:

- Adverse events that are serious, unexpected, and related or possibly related to participation in the research.
- Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
- Other unexpected adverse events, regardless of severity, that may alter the IRB's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

For these categories of events, it is not clear in the OHRP draft guidance if the rules pertaining to external and internal AE reporting to the IRB/IEC should also be applied. For example, does the guidance imply that investigators need not routinely forward all IND safety reports (e.g., serious and unexpected ADRs) or SUSARs received from sponsors to IRBs/IECs if they originate from sources external to the research being monitored by the IRBs/IECs?

Even though many AE reports received by sponsors during the course of a clinical study technically meet regulatory criteria for expedited reporting to regulators and investigators (e.g., IND safety reports or SUSARs), very few lead to modification of the study protocol or revisions of the informed consent form, or represent major safety concerns that could impact the study.

The OHRP draft guidance implies that the PI who receives external AE reports from sponsors that met regulatory criteria for expedited safety reporting should independently assess and identify relevant external AE reports that require notification to IRBs/IECs. If this is the intent, it would be helpful to define the role sponsors should/could play in helping the PI identify external AE reports that should be promptly reported to IRB/IECs. Clearer regulatory guidance on this point would be beneficial.

IV. How do you determine which adverse events are unanticipated problems that need to be reported under 45 CFR part 46?

Please refer to comments and recommendations under question III.

V. What should the IRB consider at the time of initial review with respect to adverse events?

This section outlines a detailed description of a research "monitoring plan" governing the handling of adverse events and unanticipated problems. While we agree that there needs to be good documentation of such a plan, the term "monitoring plan" has a very specific meaning to a sponsor and using it in a different context, as has been done in this draft guidance, may generate significant confusion. Many of the elements proposed to be included in the "monitoring plan" are actually defined and maintained by the sponsor in a variety of documents, including the protocol, monitoring plan, statistical analysis plan, Data Monitoring Board (DMB)/CEC charter, etc. For the purpose of this draft guidance document, we would suggest renaming monitoring plan such that confusion with a sponsor's study monitoring plan is prevented.

VI. How should reports of external adverse events, internal adverse events, and unanticipated problems be handled?

The proposal regarding the handling of "external" adverse events appears to represent a significant change to current process. It appears that the sponsor would become responsible for assessing the significance of the events and triaging which events are sent on to the IRBs. While we agree that the sponsor is probably in the best position to make the assessment and identify significant trends, BIO notes that such a process is very subjective in nature and this poses a potential risk.

To eliminate confusion over external and internal AEs altogether, BIO endorses the CIOMS VI Working Group proposal to eliminate routine expedited case reporting by sponsors to investigators and IRBs/IECs and to replace it periodic communications to investigators and IRBs/IECs, the timing of which might depend on the stage of development.

In addition to periodic reports to investigators and IRBs/IECs, there may still be circumstances when it would be appropriate to communicate important safety information expeditiously. This would depend on clinical judgment, the nature of the safety concern, and the strength of the evidence for causality. Although such safety alerts would most likely be based on aggregate data assessments, there could be well documented ICSRs that warrant expeditious communication to investigators and IRBs/IECs.

VII. What is the appropriate time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP?

BIO submits that the statements in this section are too general. In order to prompt compliance and consistency, we suggest that clearly specified reporting timeframes and expectations be put into place.

VIII. What should the IRB consider at the time of continuing review with respect to adverse events and unanticipated problems?

BIO agrees with the practical OHRP guidance pertaining to this question.

IX. What interactions should occur between IRBs and Data Safety and Monitoring Boards (DSMBs)/Data Monitoring Committees (DMCs) with regard to adverse events and unanticipated problems?

BIO agrees with the practical OHRP guidance pertaining to this question. However, please note that the procedures that ensure timely reporting of DSMB findings of PIs to IRBs are typically defined within sponsor Standard Operating Procedures (SOPs) and not within the study protocol itself.

X. What should written IRB procedures include with respect to reporting unanticipated problems?

BIO agrees with the general OHRP guidance pertaining to this question. However, one additional topic not referenced within the document but that needs to be raised for consideration are those studies wherein certain adverse events may be expected clinical outcomes. In some cases, these clinical outcomes may be predefined as study endpoints and therefore, not reported as adverse events.

In conclusion, BIO appreciates this opportunity to comment on OHRP's *Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others.* We look forward to seeing the Final Guidance, and would be glad to provide OHRP with further input or clarification of our comments.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs