BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

December 28, 2010

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

Re: Docket No. FDA-2010-D-0482-0001: Draft Guidance for Industry and Investigators on Safety Reporting Requirements for Investigational New Drug Applications and Bioavailability/Bioequivalence Studies

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry and Investigators on Safety Reporting Requirements for Investigational New Drug Applications and Bioavailability/Bioequivalence Studies*. BIO finds the Draft Guidance helpful in clarifying FDA's expectations with respect to the new Investigational New Drug (IND) safety requirements. The Agency has clearly stated its intention is to receive fewer, but higher quality IND safety reports and BIO supports the goal of ensuring that safety reports submitted during clinical trials are as useful and informative as possible. However, BIO is concerned that while the Draft Guidance and the accompanying Final Rule may internationally harmonize standard definitions for safety reporting, the requirements establish differing standards for assessing the causality between a drug exposure and a suspected adverse event and may in fact lead to divergence in reporting practices between international regions. In order to maximize compliance and reduce the risk of underreporting, we request additional clarification in the Draft Guidance on this question and ask that FDA coordinate with other international regulatory authorities in the spirit of global harmonization to develop a common approach to causality assessment.

BIO represents more than 1,100 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.

GENERAL COMMENTS:

I. Lack of Harmonization will result in Different Safety Information being Reported in Different Regions

BIO appreciates and welcomes FDA's overall effort to harmonize the definitions of *adverse reaction* and *suspected adverse reaction* with those of the International Conference on Harmonization's (ICH) guidelines on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)[1]. However, we are concerned that there are clear differences in how FDA and international health authorities interpret these terms in practice, particularly as they relate to a Sponsor's assessment of causality between a drug exposure and an adverse event.

The Draft Guidance states "that Sponsors are to report to FDA **only** if there is evidence to suggest a causal relationship between the drug and the adverse event…" (lines 263-264) and that "although the investigator's view of the causal relationship between an adverse event and the investigational drug is important, FDA believes that the Sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the Sponsor has access to serious adverse event reports from multiple study sites and is able to aggregate and analyze these reports." (Lines 569-573)

These sections imply that if an investigator reports a serious adverse event (SAE) as possibly related to study treatment, the Sponsor is ultimately responsible for deciding whether the adverse event meets the definition of a "*suspected adverse reaction*" for regulatory reporting purposes. Consequently, a Sponsor could decide *not* to report a potential suspected, unexpected serious adverse event because it disagrees with the causal attribution of the investigator, due to the Sponsor being "better positioned".

The view that a Sponsor may downgrade an investigator's causality assessment represents a significant departure from the current international standard and BIO is concerned that these provisions may lead to divergence of international safety reporting practices. For example, the international standard (or requirement in some regions) for safety reporting from interventional studies is that the most conservative causality assessment be used to determine regulatory reporting requirements. For example, the United Kingdom's Medicines and Healthcare products Regulatory Agency's (MHRA)

[1]ICH Guidelines on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, http://private.ich.org/LOB/media/MEDIA436.pdf

Good Pharmacovigilance Practice Guide[2] explicitly states that marketing authorization holders should use the most conservative assessment for expediting purposes when the investigator and Sponsor do not agree on causality for an individual event report. This would preclude the Sponsor from over-riding an investigator's assignment of positive attribution, an action the FDA's Draft Guidance deems as acceptable. In addition, the MHRA *Guide* specifies that if a case initially has insufficient data to make an assessment, or if the investigator does not supply a causality assessment, the Sponsor should consider the event to be causally related.

The Draft Guidance also provides examples (lines 54-59) of serious adverse experiences that should not be reported to FDA under the guidance. We believe that those serious adverse experiences will continue to be reported in other regions, because neither the European Union (E.U.) nor Japan have indicated that such events, particularly if considered as possibly related by the investigator, would not meet the criteria for reporting.

Consequently, to meet the requirements of U.S., European and other regulators, a single adverse event report could face opposing causality assessments and health authority reporting paradigms. This in turn would lead to divergent approaches toward the production of annual safety reports, study reports and notification of new safety issues to investigators. Given that many IND trials have sites in both the E.U. and the U.S., this approach to causality assessments will result in different safety information being provided to regulatory authorities, ethics committees, Institutional Review Boards (IRBs), and investigators in the different regions. While BIO appreciates FDA's intent to rationalize and decrease the number of meaningless IND safety reports, the Agency should be aware that multi-national Sponsors will now face both philosophical and operational challenges in an effort to meet the differing regulatory expectations of health authorities.

As such, BIO requests further clarification on the issue of how to address causality assessments, specifically in the context of whether to use the investigator's or the Sponsor's assessment of causality, in the event that the two differ. Additionally, we would appreciate FDA reaching out to its ICH partners to develop a common approach in the spirit of global harmonization.

If FDA maintains the view that the Sponsor is better positioned to assess causality of an adverse event and that it may be appropriate and even encouraged in certain situations where the Sponsor and investigator do not concur on causality, then we request that FDA please provide examples in the Final Guidance document when it may be appropriate for a Sponsor to downgrade an investigator's causality assessment. For example, where the Sponsor's assessment is that an event was most probably caused by the underlying disease and not by the investigational drug, but the investigator has stated in the report that the event is causally related to the drug, please describe the circumstances under which it would be appropriate for the Sponsor to make a downgraded causality assessment and not expedite the report to the FDA.

[2] U.K. Medicines and Healthcare products Regulatory Agency, *Good Pharmacovigilance Practice Guide*, page 39, section 3.4.2

BIO also suggests that FDA further clarify what is expected of investigators when reporting adverse events and further discuss the topic of Investigator Good Adverse Event Reporting Practices in future guidance.

II. Data from ongoing Clinical Trials should not be Unblinded for the Purpose of Completing Aggregate Analyses of Serious Adverse Events

BIO also requests additional clarification regarding the unblinding of ongoing clinical trials. For example, the Draft Guidance states "At appropriate intervals, the numbers of such events in each arm of a controlled study should be compared and reported to FDA expeditiously as an IND safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug caused the adverse event." (Lines 339-343) Further, the Draft Guidance states "The Sponsor or an independent group should monitor the identified events during the course of the trial and submit an IND safety report if an aggregate analysis indicates that the events are occurring more frequently in the drug treatment group." (Lines 365-369)

We believe the above text regarding the need to conduct analyses could be easily misinterpreted as requiring Sponsors or an independent body to unblind trial data. While we understand that this language is largely reflected in the ICH E2F Development Safety Update Report (DSUR) Guideline[3], we note that the current ICH E2F guideline includes the following language:

"Sponsors should not unblind data for the specific purpose of preparing the DSUR." (See ICH E2F; Section 3.7, third paragraph, last sentence; page 11).

As such, we recommend that FDA include the following text in the Final Guidance:

> "Sponsors should not be unblinded to clinical trial data from an ongoing trial for the purpose of completing aggregate analyses of serious adverse events, unless pre-specified by the statistical plan."

The above text should be inserted in Line 343 after the conclusion of the sentence ending in "…event." and in Line 369 at the conclusion of the sentence ending in "…section V.A.3.c]."""

We also are concerned that the Draft Guidance does not clarify under what circumstances Sponsors would be required to perform the comparisons of serious adverse events in different arms of the same study. The guidance should describe how often this type of compared group analysis should occur and what should trigger the analysis. For example, the guidance could state that Sponsors are responsible for noting the frequencies of serious adverse events being reported in a trial and should initiate a

[3] ICH Harmonized Tripartite Guideline Development Safety Update Report E2F (Step 4 version), http://www.ich.org/LOB/media/MEDIA4727.pdf

compared group analysis, probably through a Data Monitoring Committee (DMC), in cases where the overall incidence seems much higher than anticipated.

We believe this will ensure a better understanding of FDA's intent for the review of serious adverse events that are not study endpoints as well as serious events that are pre-specified in study protocols. Further, it will better harmonize FDA requirements with those of other regulatory health authorities that have adopted ICH E2F guidelines, which is one of the stated goals of FDA's current Draft Guidance (See Section II, p.1).

CONCLUSION:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry and Investigators on Safety Reporting Requirements for Investigational New Drug Applications and Bioavailability/Bioequivalence Studies*. More specific, line-by-line comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS:

SECTION	ISSUE	PROPOSED CHANGE
III. DEFINITIONS		
Lines 136-138:	The Draft Guidance document states that a causal relationship between an adverse event and a drug may be demonstrated by "one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture)."	We recommend the Agency use the statistical thresholds set out by Council for International Organizations of Medical Sciences (CIOMS) III/V when defining what FDA considers to be "common" vs. "uncommon" with respect to this point.
Lines 153-175:	This section defines the term "Unexpected" in accordance with (21 CFR 312.32(a)). Conversely, it should be clarified that adverse events (AEs) must be characterized or positioned as suspected adverse reactions in the Investigator Brochure (IB) or other reference safety information (RSI) document to be classified as "expected" for regulatory reporting purposes.	Please clarify that suspected adverse reactions should be listed in a separate section of the Investigator Brochure (IB) and characterized as "Expected for Regulatory Reporting Purposes" in that section.
IV. MONITORING THE SAFETY DATABASE AND SUBMITTING IND SAFETY REPORTS		
Lines 226-227:	FDA has clarified in both the Final Rule and the Draft Guidance document that when submitting IND safety reports to the FDA and all participating investigators; "*Participating investigators* include all investigators to whom the Sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1))." We understand this to mean that IND safety reports should be sent to all investigators in the study of origin, all investigators in any open INDs for the same ***investigational drug***, and any investigators conducting a study under their own IND to whom the Sponsor provides	Please clarify this point.

	the ***investigational drug***. Furthermore, we understand that "investigational drug" is not meant to be interpreted as ***all*** investigational drugs with the same active moiety, but rather just the form and formulation of the investigational drug in question.	
Lines 261-264:	Neither the Final Rule nor the Draft Guidance provide clarity on whether to report an event if there is not enough evidence to ***refute*** a "reasonable possibility" that the drug caused the event, particularly in situations where there is a lack of positive evidence supporting a causal relationship. For example, a recent FDA warning letter posted September 2010 cited a company for failing to report patient deaths that have "not been determined by the patient's prescriber or health care provider (or any other specific information about the death) to be non-attributable to the drugs, thus creating a reasonable possibility that the drug caused the deaths." Although this citation was made with respect to postmarketing reporting requirements is it demonstrative of how the definition of "reasonable possibility" may be executed in practice.	It would be helpful to have guidance on when to report serious, unexpected adverse events in situations where the evidence neither supports nor refutes a causal relationship.
Lines 300-397:	This section refers to various types of events that may not require expedited reporting, but that should be reported and evaluated in other ways.	For certain disease-related events that are chronic and may not change throughout the study, the guidance should clarify whether these events qualify as reportable treatment emergent adverse events; which are events that emerge during treatment having been absent pre-treatment, or that worsen relative to the pre-treatment state (ICH E9).
Lines 433-445:	A new requirement was introduced in the Final Rule and further explained in the Draft Guidance document stating that "The Sponsor must report any clinically important	Please provide an example that would demonstrate how Sponsors should define "clinically significant" in practice.

	increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (21 CFR 312.32(c)(1)(iv)).” An example involving rhabdomyolysis is given in the Draft Guidance; however, it would be more useful if the Agency provided examples demonstrating a statistical or quantifiable threshold that serves to define “clinically significant.”	
V. OTHER SAFETY REPORTING ISSUES		
Lines 449-464:	This section elaborates on alternative reporting arrangements (21 CFR 312.32(c)(3)). It would helpful to include examples of possible alternative reporting arrangements for IND safety reports. For example, would it be acceptable to provide investigators periodic summaries in the form of listings of IND safety reports or SUSARs rather than individual reports.	Please include examples of possible alternative reporting arrangements for IND safety reports.
Lines 533-535:	Both the Final Rule and Draft Guidance document state “If the blind is broken and the subject was receiving drug treatment (test drug or active comparator), the suspected adverse reaction must be reported in an IND safety report (21 CFR 312.32(c)(1)(i)).” If the Sponsor is not the market authorisation holder for the active comparator it is likely they will not have enough information to produce a thorough and complete analysis of an associated event in an IND safety report.	Please clarify if a Sponsor is to expedite reports on active comparators to the FDA as IND safety reports in situations where the sponsor is not the market authorisation holder of that product.
Lines 533-538:	The Draft Guidance states that “If the blind is broken and the subject was receiving drug treatment (test drug or active comparator), the suspected adverse reaction must be reported in an IND safety report (21 CFR 312.32(c)(1)(i))... [and] subsequent occurrences submitted	Kindly clarify that “subsequent occurrences” in this context refers to subsequent occurrences in the *same* subject and not subsequent occurrences in different subjects.

	as follow-up information to the IND safety report." It is not clear whether this point refers to subsequent occurrences in the same subject or different subjects. Subsequent occurrences in a different subject are typically submitted as separate initial IND safety reports and not just as follow-up information to the initial case, because each individual case safety report should be representative of an individual patient or subject that experienced the event.	
Lines 535-537:	The Draft Guidance also states that while events occurring in subjects receiving placebo should not be reported in an IND safety report, for events occurring in the drug treatment group "Any similar occurrences in the placebo group would be described in the IND safety report as part of the analysis of the significance of the suspected adverse reaction in light of other relevant information..."	Please provide further explanation on whether occurrences in the placebo group to be included in the IND safety report analysis are restricted only to cases that were previously unblended, but determined not-reportable because the subject was receiving placebo This would further clarify that Sponsors, in order to provide an analysis of similar events by treatment group, are not expected to unblind all previous reports of similar events that remained blinded, as they were not considered reportable.
VI. SUBMITTING AND IND SAFTEY REPORT (21 CFR 312.32(C)(1)(V))		
Lines 664-665:	The previous version of the regulations on IND safety reporting required companies to submit IND safety reports to FDA within 15 calendar days after Sponsor's *initial receipt of the information*. According to the new Final Rule and Draft Guidance document "The timeframe for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days *after the Sponsor determines that the suspected adverse reaction or other information qualifies for reporting* (21 CFR 312.32(c)(1)) [emphasis added]." This statement could be interpreted to mean that the reporting time clock now starts on the day a Sponsor's causality and	We request further explicit explanation in the Final Guidance on whether IND safety reports should be submitted within 15 calendar days after the Sponsor's *initial receipt of the information,* which is consistent with current international standards, or within 15 calendar days after the Sponsor's *determination of causality and expectedness qualifies the event for reporting* to the FDA.

	expectedness assessment is made; not the day the Sponsor initially received the information. If a Sponsor does not make a causality and expectedness assessment on the same day it receives the information, this would effectively increase the amount of time a Sponsor is allowed to submit an initial IND safety report.	
Lines: 671-673:	The Draft Guidance states "[a]ny unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the Sponsor's initial receipt of the information (21CFR312.32(c)(2)." It is unclear if the Draft Guidance suggests that a 7-day report of an unexpected fatal or life-threatening suspected adverse reaction should be followed by a 15-day report eight days later to meet FDA's IND safety reporting requirement.	We request FDA to clarify in the Final Guidance that an unexpected fatal or life-threatening serious adverse reaction submitted to FDA within 7 calendar days must also be followed by a 15-day report.
VII. FOLLOW-UP INFORMATION (21 CFR 312.32(D))		
Lines 685-688:	The Draft Guidance states "[a]ny relevant additional information that the Sponsor obtains that pertains to a previously submitted IND safety report must be submitted to FDA as a *Followup IND Safety Report* without delay, as soon as the information is available." It is unclear as written in the Draft Guidance what FDA envisions as the required timeframe for submission of the Followup IND Safety Report.	Although it may be understood that a follow-up report should be submitted in 15 calendar days, it would be helpful to state as such in the guidance.

VIII. SAFETY REPORTING REQUIREMENTS FOR BA AND BE STUDIES		
Lines 712-714:	In reference to bioavailability (BA) and bioequivalence (BE) studies, the Draft Guidance states "…the occurrence of any serious adverse event, whether or not it is considered drug-related, is of interest. Timely review of this safety information is critical to ensuring the safety of study subjects."	While we understand and support the emphasis placed on the reporting of serious adverse events regardless of causality, it is unclear from the Draft Guidance whether FDA expects Sponsors to submit reports for *any* expected or unexpected serious adverse events. We believe FDA should provide more explicit clarity in the Final Guidance.
Lines 764-766:	The Draft Guidance states "The drug product should be listed in box C1 of FDA Form 3500A; and if the serious adverse event occurs in a subject receiving the investigational drug product, the established name of the reference listed drug should be listed and identified as investigational." As written this sentence is confusing and could be easily misinterpreted.	We suggest the following edits (changes underlined): "…and if the serious adverse event occurs in a subject receiving the investigational drug product, the drug administered during BA/BE study should be identified as investigational and the established name of the reference listed drug should be listed." Additionally, the instructions in Form 3500A should be amended to include the updated language contained in the Final Guidance.