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

May 20, 2010

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **Proposed Rule: Reporting Information Regarding Falsification of Data [Docket No. FDA-2008-N-0115] 75 Federal Register 7412 (February 19, 2010)**

Dear Sir/Madam:

BIO appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) regarding sponsor reporting of falsification of data in nonclinical and clinical studies.

BIO represents more than 1,200 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 technologies, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

Given the research–intensive nature of BIO's members, the integrity and validity of data is of critical importance to us. We agree with FDA's stated goals of protecting the rights, safety and welfare of research subjects and of assuring the validity of data that the Agency receives in support of product approvals and for other purposes. We also agree that participants in the product development process can and do play a critical role in assisting FDA in detecting falsification of data.

BIO has concerns, however, regarding the broad and vague nature of the proposed rule, the lack of a threshold for reporting possible falsification of data, and the practical impact of the timing of reporting proposed by the Agency. Moreover, due to the ambiguity of the

proposal, and contrary to the statement in the preamble, the proposed rule does in fact impose significant new requirements on sponsors. These and other specific concerns are detailed below.

1. Definition of "Falsification of Data"

BIO is concerned that the definition of falsification of data is too broad. Section II.A. of the preamble, as well as the proposed regulations, *e.g*. section 312.56(e)(i), discuss and define "falsification of data" as "creating, altering, recording or omitting data in a way that the data do not represent what actually occurred." A separate part of the proposed regulations, however, states that sponsors should not "report errors (*e.g.* typographical errors, transposed numbers or characters to FDA . . ." Proposed 312.56(e)(2)). Thus, while FDA clearly intends to exclude errors, the definition itself of the critical term fails to reflect that exclusion. BIO suggests that FDA clearly exclude errors in the "Falsification of data" definition set forth at proposed 312.56(e)(1)(i).

2. Whose Falsification of Data a Sponsor Would be Required to Report

Section II.C. of the preamble to the proposed rule addresses whose falsification of data a sponsor would be required to report. BIO believes that FDA should narrow the focus of the proposed rule to sponsor reporting of data falsification by clinical investigators and other study site personnel. BIO understands investigator misconduct to be FDA's primary area of concern, based on the statements of purpose and the data falsification examples provided in the preamble to the proposed rule. Indeed, applying the reporting requirement to investigators and other site personnel would be consistent with the traditional scope of the regulations being amended in this proposal and the scope of FDA's regulatory authority in this area.

As proposed, the rule could be construed to require sponsors to report data falsification by its own employees. Since employee conduct is often imputable to the employer for both civil and criminal culpability, if interpreted in this manner, the rule would seemingly mandate sponsor companies and institutions to potentially incriminate themselves as well. While organizational entities are not accorded the same extent of constitutional protection as individuals, the government should nonetheless be reluctant in any context to make it a separate, additional crime to fail to report one's own potential misconduct. A requirement to self-disclose any identified circumstances of possible data falsification may have an unintended effect on aggressive monitoring and assessment of internal data-related activities. This may be particularly true if a reporting requirement is triggered without consideration of the significance of the falsification, of whether the data has been disclosed or submitted to FDA, or of any evidence of improper intent.

Similarly, sponsor's internal investigations of potential data falsification also may be adversely affected. Employees may be less cooperative and forthright, knowing that their name and any possible act of falsification will be sent to FDA. The proposed rule would

also interfere with the traditional protections, such as attorney-client privilege, designed to encourage client candor in seeking legal advice.

3. Proposed Requirement to Report *Possible* Falsification

Section II.F. of the preamble states that the proposed rule is intended to require the reporting of "not only confirmed, but also possible falsification." FDA expressly seeks comment on whether the regulation should specify an evidentiary standard or minimum threshold, such as what form or quantity of information would be needed to create a reporting requirement.

BIO believes the "possible falsification may have occurred standard" is too vague and uncertain and a clear threshold should be adopted in the final rule. Under the proposed rule, FDA would require that sponsors report information about whether any person has, or may have, engaged in the falsification of data in the course of reporting study results, or in the course of proposing, designing, performing, recording, supervising, or reviewing studies conducted by or on behalf of a sponsor or relied on by a sponsor. For the purposes of this proposed rule, ''falsification of data'' means creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred. FDA subsequently notes that "unintentional errors in recording and reporting information" do not have to be reported as falsification. 75 Fed. Reg. 7415. Mandating the reporting of every possible situation where someone "may have" omitted data in a clinical study is remarkably broad and unworkable. It could arguably apply to all persons and all data, regardless of circumstances. It is simply impossible, as a matter of logic, to categorically exclude the possibility that someone may have done something. Instead of requiring reporting of all information about any possible omission of data, BIO supports a "reasonable basis" standard. That is, a sponsor should be required to assess the facts and circumstances of any particular case and address whether there is "a reasonable basis derived from an appropriate investigation of the circumstances of the possible falsification, to conclude that the person's actions likely constitute falsification of data rather than error."

BIO is also concerned about the impact on individuals implicated in data falsification reports submitted to FDA where no data integrity issue, in fact, actually exists. Such reports will inevitably occur because, as discussed above, the proposed rule would require companies to submit reports based on "possible falsification"--*i.e*. unverified (and, in some cases, unverifiable) information.

The impact on individuals identified in such "erroneous" reports would be enormous, given the fact that no clinical investigator can risk, personally or professionally, being named in a data falsification report, even if the report (in fact) has no merit. No drug or biologic sponsor will employ an investigator with a potential "cloud" at FDA – the stakes are too high. Yet, as currently framed, the effect of this proposed rule would be to perpetuate suspicion within the community of clinical investigators, sponsors, and FDA, simply

because many submitted reports will inevitably just linger, with no misbehavior by an investigator ever being definitively established.

This effect of the proposed rule would be magnified significantly, given FDA's preamble statement that the Agency intends to use the information collected from sponsors to *"...identify patterns, potential signals, or other indications of misconduct, so that [FDA] can conduct further investigations."* 75 Fed. Reg. 7414. This statement is troubling indeed. Does FDA intend to maintain a database of accused investigators? If so, would the database be confidential, or would members of the public be able to access the database? Clearly there would be strong interest by various stakeholders in accessing the names any such database would contain: by drug and biologic companies seeking to avoid employing clinical scientists whose credibility with the Agency is in any way at risk, by Institutional Review Boards interested in investigator misconduct, by the media, public interest groups and plaintiffs lawyers. Due consideration needs to be given to the management and potential consequences of creating reports and the ramifications to all interested parties. Further, to the extent Contract Research Organizations have been duly delegated sponsor roles, FDA should address what if any obligations are intended to be imposed on CROs under this proposal or whether the CRO obligations can be determined solely between the CRO and sponsor.

Accordingly, BIO believes that any final rule should include a clear and transparent explanation of what information would be maintained in such a database and how FDA intends to use the information from such reports. FDA should explain whether such a database will be created, whether information on all reports would be included (or only those for which falsification of data has been confirmed), the totality of information it will contain, whether and how persons involved will have an opportunity to review and respond to information in reports, and what information, if any, would be made public. Even in any confidential FDA internal review, any such database should place the data in an appropriate context that ensures that reviewers understand that such information contains inconclusive information regarding falsifications and does not constitute evidence of confirmed falsification or culpability.

4. <u>How a Sponsor May Become Aware of Data Falsification and Timing of Reporting to FDA</u>

BIO believes that a sponsor must be given sufficient time to determine whether a reportable falsification event has occurred before it can provide the necessary information to FDA. Even under FDA's "may have occurred" standard, a sponsor will have to determine whether or not the relevant data reflect an error (which need not be reported) or a possible falsification (which must be reported). This determination necessarily requires due diligence by the sponsor into the underlying circumstances and intent of the relevant investigators. The due diligence may be comprised of a review of forms, a review of raw/source data, interviews with relevant individuals, or other activities. In instances where an error or intentional falsification is not obvious, forty-five calendar days simply

does not provide sponsors with sufficient time to perform these diligence activities and to make the appropriate requisite falsification determination.

Accordingly, BIO respectfully disagrees with FDA that 45 calendar days is an appropriate amount of time to review the information suggesting possible data falsification and to submit the necessary report to FDA. BIO agrees that reporting of falsification should be prompt, but a 45-day reporting period will not provide sponsors with sufficient time to determine whether a reportable event has actually occurred.

Instead of a restrictive timeline for sponsors to make the initial determination of whether a potential falsification event is reportable, FDA should establish a 15 calendar day timeline for reporting that begins once the sponsor has promptly determined that the threshold for falsification has been met based upon an appropriate investigation of the matter. This would mean that a sponsor would report an incident 15 days after determining that there is a reasonable basis, derived from an appropriate investigation of the circumstances of the possible falsification, to conclude that the person's actions likely constitute falsification of data rather than error. It would ensure that only meaningful data probative of falsification is submitted to FDA and would significantly minimize the amount of Agency resources necessary to further investigate reported falsification events, the likelihood of false reports (*i.e.,* persons wrongly suspected of falsification), and the unintended adverse consequences of any such false reports.

5. New Reporting Requirements/Analysis of Impacts on Sponsors

FDA states in its proposed rule that the Agency is not expecting the new regulation to result in any additional reports of falsification. Specifically, the Agency notes that it currently receives approximately 73 reports of data falsification per year, across all Centers, and that it expects to receive the same number of reports if the proposed rule is adopted. 75 Fed. Reg. at 7419.

It is not clear how FDA reached this conclusion. Existing 312.56(b) requires sponsors of *on-going* investigations to report to FDA if they (1) determine that fraud has occurred and (2) end the offending investigator's participation in the study because compliance can't promptly be secured. Yet the proposed rule effectively expands these reporting requirements into an ongoing requirement that would "cover the periods before and after study completion, including after the review, approval, or authorization of the affected product or labeling." 75 Fed. Reg. at 7413. It is unclear how the enlarged scope encompassed by the proposed rule will result in no increased reporting. Accordingly, FDA's analysis of impacts located at section VI. of the preamble is either flawed or confusing, and should be re-done, or appropriately explained.

6. Variation in Requirements for Clinical Trials with International Sites

While BIO recognizes that sponsors should be vigilant in reporting cases of data falsification, FDA has repeatedly emphasized the importance of establishing harmonized standards for clinical trials. It is preferable that any standard adopted by FDA should be established in coordination with other regulators so that there is a single standard for reporting such information in clinical trials. Under FDA's proposal, global clinical trials would be subject to one reporting standard for sites to support a U.S. approval, with different reporting standards for each geographic location of the sites in a global clinical trial. The result would be a patchwork regulatory approach, which does not make sense or best protect public health. Reasonable standards for good clinical practice, including reporting when there is a reasonable basis for concluding there has been data falsification, should be adopted globally and not promulgated separately for each country. BIO urges FDA to work with other regulators to adopt a unified standard and not to proceed unilaterally.

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BIO appreciates your consideration of these comments regarding *Reporting Information Regarding Falsification of Data* and looks forward to FDA's efforts on these issues. If you have any questions, please feel free to contact me at 202-962-6673.

Sincerely,

Sandra J.P. Dennis
Deputy General Counsel for Healthcare
Biotechnology Industry Organization