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February 22, 2011

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

Re: Docket No. FDA–2010–N–0548: Good Laboratory Practice for Nonclinical Laboratory Studies

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on "Good Laboratory Practice for Nonclinical Laboratory Studies." BIO supports FDA's initiative to revise the Good Laboratory Practice (GLP) regulations to more completely address how nonclinical studies are currently conducted, particularly in light of the fact that the regulations have not been substantially revised since the late 1970's. BIO supports a quality systems approach to GLP to ensure continual improvement and high quality lab studies, which is embodied in the current GLP regulation. Wherever possible, we also encourage alignment with international standards and principles governing the conduct of nonclinical 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 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. GLP Quality System

In general, BIO supports a quality system approach to nonclinical study conduct, and we believe that essential elements for such an approach are adequately reflected in the current GLP regulations. The FDA has previously stated that the current GLP regulations embody a quality system because they include defined roles and responsibilities; promote the quality and integrity of nonclinical studies; define the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported; and require accountability of test facility management for all GLP violations. Indeed, the benefits from the International Organization for Standardization (ISO) standard are already incorporated in the GLP regulations.

In particular, FDA is considering whether to specifically mention in the regulations, the management responsibility for all activities at a facility and whether or not a requirement for Standard Operating Procedures (SOPs) for all essential functions should be included. BIO believes that these elements of a quality management system already exist throughout the GLP regulations, including sections 58.31 and 58.81.

BIO does not believe that adding requirements that go beyond those outlined in the current regulations would further ensure the integrity of nonclinical study data. The overall goal of the GLP revisions should be to complement the controls already provided by the GLPs, rather than introduce a new layer of requirements for the Sponsors to comply with. In addition, it is important that proposed changes be consistent with requirements of other accepted quality management systems.

FDA may also want to consider that studies conducted according to US FDA GLPs may be used to support applications on a global basis, and the introduction of any new elements should be aligned with non-U.S. regulatory requirements or expectations.

II. Multi-site Studies

Drug development is often a global enterprise and BIO agrees that it is currently common practice to conduct nonclinical laboratory studies across multiple sites rather than having a single site conduct all aspects of a study. Therefore, we agree that revising the current GLP regulations to address the use of multi-site studies would be beneficial to industry. In the spirit of harmonization in a global industry, BIO recommends that any revisions made to address the conduct of multi-site studies performed at multiple sites be consistent with the Organisation for Economic Co-operation and Development ("OECD") Consensus Document 13, "The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies", and subsequent monographs. Alignment with OECD would aid in international consistency and would not unnecessarily introduce another layer of oversight beyond that required by the OECD GLPs, particularly regarding the Principal Investigator concept and responsibilities as stated in those documents.

III. Electronic/Computerized Systems

Technology and computerized systems governing SOP maintenance, data generation and capture, and training record maintenance have played an increasingly important role in GLP oversight since the regulations were published in 1978. Therefore, BIO agrees with the proposal to update the GLP regulations to reflect the use of electronic/computerized systems. However, we feel that such modifications in requirements should be general enough to accommodate changes and evolution in technology.

Certain paper-based processes continue to co-exist with electronic systems. The GLP Regulations as a whole should be reviewed to include language that would be suitable for both paper and electronic process/systems to accommodate the current diversity of raw data. For example, we agree that sections 58.35(b)(1) and (b)(2) should be modified to require the Quality Assurance Unit (QAU) to have access to, but not maintain, copies of the Master Schedule and all protocols.

BIO feels the GLPs should allow for more than one individual to be assigned as an archivist. One individual may not have the expertise to properly archive and retrieve all types of raw data, (*e.g.*, paper, specimens, and electronic data). As a result, there may be the need for special knowledge and expertise in handling these items. Allowing for more than one archivist could provide a reasonable solution to the problem without compromising the quality and integrity of the data.

IV. Sponsor Responsibilities

BIO does not believe that including additional specific responsibilities of Sponsors of nonclinical laboratory studies will improve the quality and integrity of nonclinical laboratory study conduct. The current GLP regulations require the Sponsor to approve nonclinical laboratory protocols prior to study initiation (section 58.120(a)). Once the study is initiated, the Study Director is the single point of control. This requirement, complemented by test facility management responsibilities (section 58.31) and other requirements outlined in the current GLPs, should be sufficient to ensure the quality and integrity of nonclinical study conduct.

V. Animal Welfare

BIO supports the goal of ensuring the welfare of research animals and using animals for research only when no scientifically valid alternative to animal use exists. We feel the current GLP regulations, coupled with the FDA's *Bioresearch Monitoring Good Laboratory Practice Compliance Program Guidance Manual 7348.808* (Section 7), already direct investigators to review, observe, and inspect animal care activities, and that additional oversight by FDA is unnecessary.

BIO believes that the Department of Agriculture (USDA) should continue to exclusively oversee the animal programs that have GLP programs. The USDA currently performs unannounced inspections of research facilities and generates inspection reports. The FDA has access to these documents and can review the observations and concerns brought forth by the USDA. Additionally, Institutional Animal Care and Use Committees (IACUC) monitor animal welfare via

the review of study designs, the inspection of facilities, and the approval of humane endpoints. Documentation of IACUC activities and concerns is also available for FDA review. It is beneficial that these programs be accredited by Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

Revising the GLP regulations to include additional FDA oversight in the above areas would result in redundancy and overlap with USDA functions, and would be inconsistent with the Presidential Executive Order on *Improving Regulation and Regulatory Review*, dated 18 January 2011. Therefore animal welfare should be out of the scope of the FDA GLPs.

VI. Information on Quality Assurance(QA) Inspectional Findings

BIO believes that adding a requirement for the Quality Assurance Unit (QAU) to prepare an annual summary of general inspectional findings that would be available for FDA review would jeopardize the original intent of the QA role and process. BIO would like FDA to consider whether the information in this summary is already covered by the requirement for periodic status reports. The ability of the QAU to provide independent regulatory oversight for GLP studies is an important aspect of the current regulations. For example, the regulations already require availability of the study inspection dates, phase or segment of the study inspected, and the name of the individual performing the inspection, and they address management responsibility for corrective action (section 58.35).

Additionally, QA should be able to inspect any phase of a study, any process, and any nonclinical laboratory without concern of QA findings becoming public information or fear of interference from management. Requiring the availability to FDA of additional information from these internal audit documents may discourage candid detail within the reports and weaken the process as an effective and efficient quality management tool. The effect of this reporting on the confidentiality of Sponsor data must also be considered.

VII. Process-Based Systems Inspections

BIO agrees that performing process-based inspections for procedures commonly performed across many studies is an acceptable method for managing resources while not sacrificing the quality and integrity of the study. Therefore, we agree with FDA's recommendation to consider formally allowing for a combination of process-based systems inspections and study-specific inspections to accomplish the responsibilities of the QAU.

However, we feel that referencing the results of these process- based inspections in study-specific inspection reports would impose an unnecessary administrative burden that would not enhance the quality and integrity of the study. BIO believes that any changes regarding process-based inspections should be harmonized with OECD principles of GLP. Changes made to allow for process-based inspections should allow for these to be performed in lieu of the requirements to inspect each nonclinical study.

Sponsor confidentiality must be maintained with respect to quality reporting for processes across studies.

VIII. Test and Control Article Information

BIO supports FDA's proposal to accept test and control article characterization performed in a Good Manufacturing Practice (GMP) laboratory. BIO believes that clarifying the GLP regulations to indicate that it would be acceptable to generate test article characterization data in compliance with Current Good Manufacturing (cGMP) regulations would be a valuable improvement. However, in regard to including timeframes for provision of this information to the Study Director, requiring characterization before study initiation may not be reasonable. We feel that the Sponsor has the responsibility to ensure this information is provided to the study director for inclusion in the final report. Therefore, we believe adding a requirement that includes defined timeframes for providing this information to the study director would not add value to the GLP regulations.

IX. Sample Storage Container Retention

BIO Agrees with FDA's proposal to eliminate the requirement in section 21 CFR 58.105(c) to maintain test article storage containers for the duration of the study. The requirements of §58.107(d) provide adequate information about the use and integrity of study samples and that eliminating the requirement of §58.105(c) to maintain test article storage containers for the duration of the study will not adversely affect the quality, integrity, and reconstructability of nonclinical laboratory studies.

X. Draft Contributing Reports

BIO is aware of concerns raised in a variety of venues regarding the use of draft contributing scientist reports for initiating the drafting of the final study report. BIO believes that given the complexity and specialization of nonclinical studies, it is beneficial for different types of knowledge and expertise contribute to addressing and interpreting the data. Collaboration among scientists contributing to the study report is essential in order to have the most accurate and scientifically sound report.

BIO feels the current GLP regulations adequately address the requirements for final report preparation. Internal procedures should ensure all contributing scientist reports are signed prior to the study director signing the final report. Additional assurance that the final report accurately reflects the raw data is provided in the form of QAU audits. If a more iterative report generation process is used wherein signed contributing scientist reports must first be issued, the entire drug development process will become more protracted. Thus, BIO members' ability to clinically evaluate and provide therapeutic advances to patients will most certainly be prolonged.

CONCLUSION:

BIO appreciates the opportunity to provide comments regarding proposed changes to the regulations governing "Good Laboratory Practice for Nonclinical Laboratory Studies." As the Agency moves forward in revising the GLPs, consistency with other Agency regulations such as Environmental Protection Agency (EPA) GLPs, 21 CFR Part 11, the USDA Animal Welfare Act, and OECD GLPs should be a prime consideration in order to minimize the overall impact of any regulatory revisions and to assure the quality and integrity of future nonclinical laboratory studies. 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)