Biotechnology Industry Organization
1225 Eye Street NW, Suite 400
Washington, DC 20006

December 3, 2004

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

Re: Docket No. 2004D-0443, CDER 2004115. Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations; Availability.

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 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. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Draft Guidance for Industry on a Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.

General Comments

We support FDA's efforts to refine and update cGMP regulations and inspectional practices based on changes in technology and business. Development and implementation of effective quality systems are important to the pharmaceutical industry as we move into the 21st century. However while this document may be valuable for a company initially setting up a quality system, it does not provide much additional information for implemented systems. It is not clear how this document provides clarity regarding interpretation or implementation of cGMP regulations, or how it provides for a regulatory environment that supports continuous improvement. Therefore, while the

draft guidance may be a useful tool for some, it is questionable whether the guidance will have widespread utility for industry as written.

There are many points in the guidance where the term “recommends” is used to describe an expectation. Throughout the document it should be clarified what is expected and what is recommended.

Specific Comments

Section I – Line 18 (change). It would be helpful for FDA to define the adjective “modern” as it applies to quality systems or replace with the term “effective.”

Section II A – Lines 59-60 (clarification). Please reconcile FDA’s intention to use this guidance to supplement the cGMPs with Quality System requirements as implemented in the medical device area (21CFR820), in contrast to the statement in lines 24-25 that this guidance "is not intended to place new expectations on manufacturers."

Section II B – Lines 92-94 (clarify). One of FDA's stated reasons for this guidance is to "harmonize the cGMPs...and FDA’s own medical device quality system regulations." The guidance format is not an appropriate means of harmonizing regulations or revising regulations. We ask FDA to comment on this stated purpose and how it is consistent with the statement in lines 24-25 that this guidance "is not intended to place new expectations on manufacturers."

Section II B – Line 98 (change/add). To make the guidance more specific, it would be helpful to modify the line as follows: “certain types of improvements without the need for a prior regulatory filing. Sufficient process knowledge enables classification of proposed changes into three categories: 1) Those that can me managed within a firm’s quality systems, 2) Those that are appropriately performed under an approved comparability protocol, and 3) Those that require a pre-approval supplement.”

Section II C - Page: 2
Line 112 (insertion). To emphasize the perspective of management of change lines 125-6 should be moved here.

Section III – This section is a general overview of the current state of affairs. It is not clear how this provides guidance to Industry.

Section III B - Page: 2
Line 166 (add). “… products.” For example, with the production of components such as biologically-derived macromolecules, consideration of comprehensive quality systems and the aspects of *quality by design* discussed herein are generally recognized as relevant.

Section III C – This section could provide more information regarding expectations for risk assessment and management.

Section III E– Lines 196-198 (clarification). FDA addresses "...creating a regulatory environment that encourages change towards continuous improvement. This means a manufacturer is empowered to make changes based on the variability of materials used in manufacturing and optimization of the process from learning over time." We ask FDA to provide a discussion of the regulatory environment where these changes are possible outside of existing regulations and guidance. It clearly applies to PAT initiatives, but they will likely be limited both in scope and in the number of companies who incorporate them and thus are not broadly applicable. Please address how implementation of "continuous improvement" is encouraged and supported in 21CFR314.70 and in existing FDA guidances on post approval changes. Is industry to consider that this regulation and existing guidance (SUPACs and other) will be substantially revised?

Section III E - Page: 3
Line 199 (add) **"…** make data driven changes"

Section III F – Some tasks are broken out between QA and QC while others are together as a responsibility of the quality unit. It is not clear if FDA is trying to recommend how industry should allocate responsibilities in the Quality Unit. If so, all responsibilities should be allocated. Also, trend analysis can be performed by the QC unit. Does that violate the expectations of the guidance? The Scope of the Guidance section states that this guidance does not create new expectations, but delineating specifics for QA and QC could be interpreted as creating new expectations.

Section IV - Line 291 (add) "…regulations." The utility of the quality systems model is for the manufacturer, and this guidance does not suggest development of new quality elements or models directly subject to regulatory and inspection coverage.

Section IV A - Define "Management" as there are usually multiple layers of management in an organization.

Section IV A 1 - It may be helpful to add expectations for training and consequences of non-compliance.

Section IV A 1 – Line 327 (clarify). It is not clear how FDA would like management to show "strong and visible support."

Section IV A 2 – Line 341 (add). Responsibilities and authorities should be documented through job descriptions and organization charts. Structure of the organization should include information on conflicts of interest.

Section IV A 3 – Line 356 (edit). The term "recommends" should be revised to strengthen the concept that Senior Management is ultimately responsible.

Section IV A 3 – Line 367 (edit). The term "recommended", in practice, is really "expected."

Section IV A 4 – Line 396 (edit). The term “recommended” should be replaced with “expected.”

Section IV A 5 – This section provides much more detail on expectations. It would appear that some of these details are options for Industry to consider. For example, on line 420 it may not be appropriate for FDA to suggest agenda items and this not really implied in part 211.

Section IV B 3 – Line 504 (clarify). It is not clear what a generic quality system model is. It may be best to define the standards versus compare them to the generic quality system models.

Section IV B 4 – Line 518 (add) “…qualified through an on site audit.”

Section IV B 4 – Lines 521-522 (clarification). It is unreasonable to expect that senior company officials of a large multi-national pharmaceutical company are "...familiar with the specifics requirements of the contract." The appropriate management needs to be well informed but this often stops far short of the office of the most senior officers in the organization. Assignment of business responsibilities does not seem to be within the range of application of GMP.

Section IV C 2 – Line 589 (edit). The term “should be” is actually an expectation.

Section IV C 3 – Line 628 (edit). The term “recommended” is actually an expectation.

Section IV C 4 – Line 660 (add) “… continues through process monitoring and trending to ensure that the validated state is maintained after the formal validation exercise.” This may also provide the basis for change management to effect improvements.

Section IV C 4 – Line 733 (edit). The term “recommends” should be replaced with “expects.” Also, it may not be acceptable to statistically invalidate test results. This concept should be deleted from this guidance.

Section IV D 2 – Line 819 (add). It is acceptable for a company to refuse an FDA request to copy internal audit reports.

Section IV D 3 – Line 837 (add) “ … manage and control change.” It is also useful to document the nature of the data upon which the risk assessment was made. This helps to capture process understanding and may help to identify opportunities for improvements.

Definitions – Line 1084 (add) “ …senior management is ultimately responsible for quality.”

Thank you for providing us with the opportunity to begin the dialogue by commenting on this Draft Guidance. We look forward to additional opportunities to discuss the matters outlined above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs