March 20, 2006

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0286
Draft Guidance for Industry — Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) "Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1." BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States (U.S.) and 31 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products.

BIO commends FDA for preparing this draft guidance, as we agree that there should be an incremental approach to manufacturing controls during investigational product development. However, we would like to offer the following comments and requests for clarification.

General Comments:

While this draft guidance is helpful, it provides limited regulatory relief to fully integrated pharmaceutical companies, large or small, that produce material for both Phase 1 and later phase clinical development. Few pilot plants or contract facilities are restricted to production of Phase 1 material, and often the material used to initiate Phase 1 studies is used in Phase 2 evaluations. Thus, for those integrated companies that move

products to later phases and commercialization, there is no relaxation of burden because Phase 1 and 2 material is often made in a single campaign, and these companies generally do not have facilities devoted exclusively to manufacturing for Phase 1. Therefore the draft guidance appears to provide value primarily to a limited subset of manufacturers with most of the relief going to academic organizations, government laboratories, and small virtual companies that would not normally progress development beyond Phase 1. We request that FDA move forward with the development of additional guidance and/or regulations to define the CGMP requirements for producing investigational drugs for Phase 2 and 3 clinical studies.

We also note that many BIO member companies and organizations evaluate investigational medicinal products in both the U.S. and the European Union (E.U.), and that the E.U. regulations and expectations are different from those described in this draft guidance. BIO requests that FDA work with European counterparts to ensure that E.U. requirements for manufacturing practices are aligned with FDA requirements.

We appreciate that this draft guidance is intended to decrease the regulatory burden to industry, while ensuring safety of research participants in Phase 1 studies. However several elements of the draft guidance may cause an increase in the regulatory burden for many biotechnology and pharmaceutical companies, without increasing product quality and safety. Specifically, the following FDA recommendations may be interpreted to require specific new documents or reports that are additive to sponsors' existing documentation of CGMP compliance activities in Phase 1:

- "formal evaluation" of the production environment (line 205)
- establishment of production controls based on a "risk assessment" (line 211)
- establishment of a "QC [quality control] plan" (line 226)
- "periodic … reviews" of the production process and product quality (line 498)

Specific Comments

Page	Section	Line	Recommendation
OVERALL			Please define what is meant by "Quality Control." Alternatively, we suggest that FDA substitute the term "Quality Unit" as this more accurately reflects the organization in most companies. "Quality Control" may be misinterpreted to refer to the quality control laboratory.
1	I Introduction	31	Please clarify what is meant by "most investigational drugs" by referring to the explanation given in the Scope section of the guidance. The sentence could be rephrased to read: ". . . most investigational drugs (see Scope section)

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			manufactured for use during Phase 1 development."
2	II Background	68	We suggest that the information in footnote 4 – stating the possibility of additional FDA guidance in the future regarding Phase 2 and 3 CGMP expectations – be moved up into the body of the text at line 68. For example a supplemental last sentence in line 68 could specify clearly that FDA is planning to issue additional guidance and/or regulations on this topic. The new sentence could be phrased to read: "To reinforce FDA's expectations for an incremental approach to manufacturing controls during clinical development, we will develop additional guidance and/or regulations to define the CGMP requirements for producing investigational drugs for Phase 2 and 3 clinical studies."
2	II Background	75	Please clarify what is meant by "certain exploratory products" by referring to the explanation given in the Scope section of the guidance. The sentence could be rephrased to read: "As the new rule specifies, the particular requirements in Parts 211 (21CFR211) need not be met for most investigational drugs (see Scope section) manufactured for use during Phase 1 clinical evaluation."
3	II Background	80-81	FDA states that "Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable." Please clarify the intent of this sentence. Without additional explanation, the sentence could be interpreted to mean that Phase 2 and 3 CGMP expectations are not different from commercial CGMP expectations. This interpretation would not be consistent with FDA's expectation for an incremental approach to manufacturing controls as mentioned earlier in this section. The sentence could be rephrased to read: "Aligning with FDA's expectation for an incremental approach

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			to manufacturing controls during clinical development, Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable."
4	V. Recommendations for Complying with the Statue	158-159	Please clarify what is meant by "most phase 1 studies" by referring to the explanation given in the Scope section of the guidance. The sentence could be rephrased to read: "These recommendations are designed to provide approaches to CGMP that appropriately address factors associated with the production of clinical supplies for use in most Phase 1 clinical studies (see Scope section)."
6	V. Recommendations for Complying with the Statute	205	FDA recommends "a formal evaluation of the production environment to identify potential hazards." Please clarify the intent of this recommendation, and the intended meaning of the word "formal." At Phase 1, the evaluation of the production environment is not necessarily recorded in a single written document. We are not sure whether FDA is setting the expectation that such a document is required; if so the recommendation appears to increase regulatory burden.
6	V. Recommendations for Complying with the Statute	211-212	FDA states that "Producers should establish production controls based on a risk assessment ..." Please clarify the intent of this recommendation. At Phase 1, risk assessments and risk mitigation activities are not necessarily recorded in a single written document. We are not sure whether FDA is setting the expectation that such a document is required; if so this expectation would increase rather than regulatory burden. The last two sentences of this paragraph could read: "At Phase 1, manufacturing controls are primarily aimed at ensuring subject safety. Producers should establish controls for the product and manufacturing process that are appropriate to the stage of

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			development, and follow good scientific and quality control principles when implementing specific practices and procedures for CGMP."
6	V. Recommendations for Complying with the Statute	226	FDA recommends "that every producer establish a QC plan and document that plan in writing." We ask that FDA clarify that a single written document entitled "QC plan" is not an expectation. Rather, there are alternatives for meeting this need, such as a Quality Manual, Quality Policy(ies), or Standard Operating Procedures (SOPs) that delineate specific Quality Unit responsibilities. This sentence could be revised to read: "We recommend that every producer identify in writing the responsibilities of the Quality Unit."
7	V. Recommendations for Complying with the Statute	247-248	FDA states that "it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch." We ask for deletion of this recommendation. Its inclusion implies approval of an approach that is in conflict with GMP expectations requiring that production and quality functions be performed by different personnel.
7		256	BIO recommends that FDA clarify what criteria might be used to determine "adequate" work areas and equipment. The sentence might be reworded to read: "Any facility, including a laboratory, used for production of investigational drugs for Phase 1 studies should have controls for the work areas and equipment related to the intended use of the product and should minimize the risk for cross contamination."
7	V. Recommendations for Complying with the Statute	280-282	FDA states that "Information to record would include receipt date, quantity of the shipment, supplier's name, component lot number, investigational product batch number ..."

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			BIO requests that FDA delete the recommendation that investigational product batch number be included in a component log-book. Generally, raw materials are used as components in manufacture of multiple products, and in most cases it is not known what those products will be at the time components are received. Therefore FDA's requirement to record investigational product batch number would typically be infeasible to comply with at the time raw materials are received. In addition, it is not clear why a component log book would be a best practice for ensuring/documenting control of components used in production of an investigational product, as opposed to other tracking methods. We suggest that instead of providing a list of information to be recorded in a component log book, FDA indicate its expectation that the manufacturer will be able to provide relevant information (such as supplier, receipt date, storage conditions) for raw materials that have been used in manufacture of the product (API, intermediate, drug product).
8	V. Recommendations for Complying with the Statute	305-306	FDA states that written production procedures should provide (among other things): "A record of laboratory testing and production data that details the components, equipment and procedures used." We recommend that this sentence be revised to read: "A record of production data that details ..." This section addresses production, not laboratory testing. Laboratory testing should be included in section F beginning with line 318.
8	V. Recommendations for Complying with the Statute	316	We ask FDA to emphasize that the Sterile Products guidance applies to drug products only and not APIs unless the API is claimed to be sterile.
8	V. Recommendations for Complying with the Statute	322-324	FDA states that "Analytical tests used in production (e.g. ...) should be scientifically sound (e.g., specific, sensitive, and accurate) and reproducible for the specified purpose." We suggest the elimination of the term "reproducible" to avoid confusion. The term "reproducible" is defined in the International

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			Conference on Harmonisation (ICH) Guideline Q2A/B to mean "the precision between laboratories (collaborative studies, usually applied to standardization of methodology)." Therefore the term "reproducible" is appropriate for the commercial setting rather than in Phase 1 testing where only one laboratory may be involved. This sentence could be revised to read: "Analytical tests used in production (e.g., ...) should be scientifically sound and appropriate for the intended use."
9	V. Recommendations for Complying with the Statute	339-341	FDA states that "When feasible, we recommend that the sample consist of twice the quantity necessary to conduct release testing (excluding any testing for pyrogenicity and sterility)." It is not always possible to allocate twice the amount of samples just for retained samples, particularly for products that are highly individualized (e.g. anti-idiotype antibody to an individual specific B cell idiotype). This sentence should be revised to read: "We recommend that the sample consist of a quantity adequate to perform additional testing or investigation if required later."
9	V. Recommendations for Complying with the Statute	374	FDA uses the phrase "All quality control functions." We request deletion of the word "all" because it is not appropriately descriptive. Instead, we ask FDA to specify which documentation is required. Further (as noted earlier) "quality control" may be interpreted to apply only to laboratory activities, so we suggest that this bullet point be revised to read: "Quality Unit functions"
11	VI. Special Production Situations	449	BIO suggests that FDA emphasize the importance of proper storage of retained samples so they may be useful and valid in future investigations and comparison studies, if necessary.
12	VI. Special	498-	FDA states that "When producing multiple batches

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	Production Situations	501	of the same investigational product, we recommend that producers periodically conduct and document internal performance reviews. We recommend that such a review assess the control and consistency of the production process and overall product quality." BIO requests that FDA eliminate this recommendation. Current IND regulations (21CFR312.33) require that annual reports be made to FDA that include a summary of any significant manufacturing or microbiological changes made during the past year. A periodic quality review is not a statutory requirement until commercial product approval (21CFR211.180(e)). While most commercial manufacturers perform this type of review as part of process development, requiring separate reports for Phase 1 production would increase burden to industry, while having no impact on product quality or safety.
13	VI. Special Production Situations	516	FDA refers to "an air classification of Class 100." BIO advises that this be reworded to read: "an air classification of Class 100 that is equivalent to ISO 5."

BIO appreciates this opportunity to comment on FDA's "Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1." We look forward to seeing the Final Guidance, and would be glad to provide FDA with further input or clarification of our comments.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs