Biotechnology Industry Organization
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5 December 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 2003D-0349, Federal Register: August 18, 2003 (Volume 68, Number 159, Pages 49488-49489)

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 health-care, agricultural, industrial and environmental biotechnology products. We appreciate the opportunity to comment on the Food and Drug Administration's (FDA's) draft *Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug (IND) Applications.*

General Comment

Overall, the guidance is well composed, providing good definitions of proposed changes and requirements. However, we believe it is important to clarify whether this guidance was intended solely for the initial IND of a product or for the entire development process, barring BLA submissions. The inclusion of end of production cell testing (Section III-A-3-a on p. 16), which is generally performed later for process validation purposes rather than as part of the initial IND, is one section among several that suggest the potential for multiple uses of this guidance by the FDA. If the guidance is intended for the different

phases of development, additional language should be added to clarify what is expected when, specifically by expanding Appendix B "Review Considerations for Development of Final Product Release Criteria Specifications and Stability Protocols." In addition, due to the sensitivity of biologics, BIO recommends that increased emphasis be placed on the chain of handling from manufacture to use, including methods of transportation as well as storage.

In terms of formatting it would be helpful if there were a consistent use of the terms "ensure" and/or "insure," and consistent alignment of the language and section numbers.

Detailed Comments

BIO's detailed comments and proposed changes to the draft guidance are given below. Underlined text is our suggested additional or alternative language.

Location	**Comments/Proposed Changes**
II, A, 1, a. p. 4 Allogeneic and/or Autologous Cell Components	The rules for (hematopoietic) cell transplants developed by the Foundation for the Accreditation of Cellular Therapy (FACT, formerly FACHT) are now standard for stem cell transplant centers. BIO encourages FDA to acknowledge these standards and use them as part of its review processes. Information about FACT can be found at its website, www.factwebsite.org.
II, A, 1, a, 2nd bullet. p. 4 Mobilization protocol	"… Document whether or not donor cells are mobilized or activated *in vivo* in the donor <u>and how this is documented by the sponsor</u>"
II, A, 1, b, 1), 6th bullet, 3. p. 7	Please provide additional guidance on what data is expected to demonstrate genetic and phenotypic stability for Master Cell Banks (MCBs) after multiple passages. Many sponsors and clinical research organizations (CROs) testing laboratories are not clear on expectations.
II, A, 2, b. p. 9 Qualification Program	"…The appropriate extent of testing will depend on where in the manufacturing scheme the specific reagent is used <u>and the residual levels in typical batches</u>."
II, B. p. 12 Product Manufacturing-Procedures	"…you should include a detailed description of all procedures used during the <u>collection</u>, production<u>,</u> and purification of the cellular therapy product."

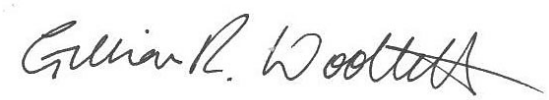
Location	**Comments/Proposed Changes**
II, B, 1, a. p. 12 Method of Cell Collection/ Processing/ Culture Conditions	"…The review should document the volume and number of cells collected. Also, document information on location for collection and processing of cells. You should include …"
II, B, 1, a. p. 12 Method of Cell Collection/ Processing/ Culture Collections	BIO suggests that the sources of the allogeneic cells and proper informed consent records should also be documented.
II, B, 1, c. p. 12 Process Timing & Intermediate Storage	BIO suggests that the following point be inserted in this section: "d. Review documentation of chain of handling from collection through administration to patient."
III, C, 1. p. 17 Residual Contaminants	Potential contaminants such as beads and plastic debris are not mentioned in this section. BIO believes that documentation of tests for such contaminants should be required.
III, D. p. 18 Potency	A validated potency assay based on function is not always available prior to administration of a product to patients. The example of biological function assay given was a proliferation assay, but due to the length of time needed for a proliferation assay, a surrogate marker assay using flow cytometry is typically used instead. Please clarify whether choice of biological function assay is open to discussion and agreement between the FDA and sponsor early in the clinical development process.
VI, B p. 21 Labeling	In the third-to-last sentence (beginning "For autologous cell therapies…") the use of both the terms "autologous" and "donor" is confusing, because "autologous therapies" refers to procedures in which the donor is also the patient/recipient. BIO suggests that the term "donor" be changed to "patient."

Location	**Comments/Proposed Changes**
Appendix A. p. 29 Tabulation of Reagents Used in Manufacture	BIO suggests that the column headed "Specify Final Concentration" should also require identification of the step at which concentration was measured.
Appendix A. pp. 28-29 Product Manufacturing – Procedures	In addition to the subsections on Preparation of Autologous or Allogeneic Cells, Final Harvest, and Final Formulation, BIO suggests the addition of a subsection entitled "Areas of Concern for Procedures."
Appendix A p. 29 Storage Method Prior to Use	BIO suggests that this heading be changed to "Storage Method Prior to Use / Transportation to Clinical Site."
Appendix A p. 29 Tabulation of Tests, Manufacturing Step, Test Methods, Test Sensitivity & Specificity, and Criteria	BIO suggests that this table be expanded to include more specific categories. In Table 1 in the Appendix to this letter, below, we give suggestions for expanding the table.
Appendix A. p. 29 Final Product Release Criteria/Specifications	In addition to the subsections on Tabulation of Final Product Release Criteria Tests [. . .] and Description of Test Methods, BIO suggests the addition of a subsection for "Notification Process," so that a chain of contacts is established for reporting of results.
Appendix A. p. 29 Tabulation of Final Product Release Criteria Tests, Test Methods, Specification, Test Sensitivity & Specificity	BIO suggests the addition of a column "Performed Prior to Administration" at the right end of the table.
Appendix A. pp. 29-30 Product Stability	BIO suggests that a table format for the reporting of the Stability Protocol would be more useful for displaying critical stability testing methods and results. In Table 2 in the Appendix to this letter, below, we give a sample structure for such a Stability Protocol Tests Table.

Location	**Comments/Proposed Changes**
Appendix A. p. 30 Product Tracking	BIO suggests that this heading be changed to "Product Tracking, Procedures and Adequacy."
Appendix A. p. 30 Container Closure & Integrity	BIO suggests that this heading be changed to "Container Closure & Integrity & Compatibility."
Appendix A. p. 30 Validation of the Manufacturing Process	BIO suggests that this heading be changed to "Validation of the Manufacturing Process and Facility."
Appendix A. p. 30 Biostatistics	An outline of biostatistics is not really needed for a Phase I IND. BIO suggests that this section be removed.
Appendix A p. 30 Genetic and Biochemical Testing	BIO suggests that this heading be changed to "Genetic and Biochemical Testing (Clinical Trial Assays)."

BIO appreciates this opportunity to comment on this draft guidance. We look forward to seeing the final guidance, and would be glad to work with the FDA to provide further input or clarification of our comments as needed.

Sincerely,



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Encl. Appendix: BIO's Suggested Modifications to FDA Draft Guidance 2003D-0349 Appendix A

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Table 1

BIO's suggested amendments to Tabulation of Tests, Manufacturing Step, Test Methods, Test Sensitivity & Specificity, and Criteria (p. 29 of Appendix A – cf. comment regarding "Tabulation of Tests, Manufacturing Step, …" on p. 4 of this letter)

Test	Method	Specification	Manufacturing Steps Where Performed	Sensitivity	Specificity
Sterility					
Mycoplasma					
Adventitious Agents (viruses)					
Purity (endotoxin)					
Purity (other contaminants; residuals)					
Identity					
Potency					
Others (cell number, dose)					
Others (cell viability)					

Table 2

BIO's suggested format for new Stability Protocol Tests Table (p. 29 of Appendix A – cf. comment regarding "Product Stability" on p. 4 of this letter)

Test	Method	Specification	Sensitivity	Stability Indicating?