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April 16, 2009

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

Re: Docket No. FDA-2008-D-0659. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).*

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.

We have provided General Comments immediately below, and Specific Comments in Appendix 1.

GENERAL COMMENTS

In general, the draft guidance contains appropriately detailed and useful information for manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps). To enhance the current draft, we have the following recommendations:

a) Differentiation among product types

To ensure clear interpretation and rational nomenclature, we encourage FDA to ensure the recommendations in the Guidance are appropriate to the intended audience, i.e., establishments that must comply with Current Good Tissue Practice (CGTP) requirements under 21 CFR part 1271, subparts D and E. For example, at times the draft seems to use language that is more appropriate to the traditional hematopoetic cells or tissue based products that are infused to approximately 1-100 different recipients. However, novel cell-based products currently in development could reach thousands to millions of recipients (please see our comments regarding the phrase "final disposition" in section c) below). This is one of many differences among product types that should be reflected and addressed in this and future guidance documents.

b) Cross-referencing of other applicable guidance

We recommend that existing guidance/regulations be referenced in the appropriate sections and included in Section XXIV. For example, Section XIII provides information related to processing and testing to avoid pathogenic microbial organisms but lacks cross-reference to guidance(s) providing information regarding appropriate testing for adventitious agents, including viruses and mycoplasma, e.g. "*Guidance for Human Somatic Cell Therapy and Gene Products*," March 1998. As another example, Section XXII pertains to adverse event reporting and should reference "*Guidance for Industry, MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*".

c) Specificity regarding the establishment and maintenance of a quality program, training (Section V, G)

The draft guidance states that "personnel involved in activities related to core CGTP requirements have proper training, education and experience to perform those activities" (p. 15), but would benefit from more specificity. For example, the document states that it is the responsibility of the sponsor to investigate and investigations of adverse events where there is an allegation of the transfer of a communicable disease from donor to recipient, but does not indicate the training required to perform such investigations. For allogeneic products, there is a high price to be paid for inadequately performing these investigative functions, as thousands of patients may be exposed to a communicable disease from one donor. The responsibility for diagnosis or investigation of a communicable disease from donor to recipient should fall upon a qualified physician, and preferably upon a physician with specialty board certification in Family

Practice or Internal Medicine or with sub-specialty board certification in Infectious Diseases and who has adequate knowledge of relevant federal regulations and guidance.

d) Tracking (Section XX)

This section places substantial responsibility on the manufacturer. We request further clarity regarding the scope of the manufacturer's responsibility in relation to other entities involved in the manufacturing process. Specifically, we recommend that the guideline clarify that each entity performing a step in the manufacturing process must create and verify its tracking system, and develop a compliant process.

In addition, we note that the meaning of the phrase "final disposition", as used in this section, is unclear. If this section is making a recommendation to track every treated patient, this would raise major concerns regarding protection of patient privacy. Furthermore, the number of patients that would need to be tracked for a mature product would be very high; for cell therapy products, the number of patients for whom prescription data would have to be managed over the life of the product could be on the order of millions of recipients. We request FDA to clarify that "final disposition" does not mean that every treated patient must be tracked by the manufacturer.

CONCLUSION

BIO appreciates this opportunity to comment on the draft guidance *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).* We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science & Regulatory Affairs
Biotechnology Industry Organization

APPENDIX 1

SPECIFIC COMMENTS

Relative Impact ***C** = A critical concern that must be addressed*
***M** = A minor concern that should be addressed*
***E** = Editorial comment to text (change not necessarily required)*

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
IVA, B, C page 10	C	Establishments performing manufacturing steps for clinical material are not required to register. The process of a request for an exemption identifies the establishment as needing to be 'registered'. How would a manufacturer of clinical material request an exemption?	Please clarify what an unregistered establishment (or an establishment with an inactive registration) would need to do if requesting an exemption.
V, E page 12	C	This section specifies the sponsor's obligation to share information regarding contamination or communicable diseases with other establishments that are known to have procured HCT/Ps from the same donor. This may be impossible if said donor were to donate tissue or cells in the future. A sponsor cannot be expected to track all future donations of HCT/Ps.	We recommend changing the wording in bullet #1 as follows: • other establishments that are known to have recovered HCT/Ps from the same *cadaveric* donor *or the same living donor during the same operative procedure* (§ 1271.160(b)(2)(i)); and

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
V, G page 13	C	The document is vague regarding specific qualifications for personnel involved in activities related to core GTP requirements. Of particular concern is the qualifications needed for determination of donor eligibility, which should be done by a health care professional who has the professional training to diagnose a communicable disease by review of symptoms, signs and laboratory results. Similarly, a comprehensive investigation of a complaint or adverse reaction related to a possible communicable disease (XXII, D, page 55) must be executed by someone who has the training and experience to review and interpret clinical records, including pathology reports, laboratory results, and medical/surgical interventions.	We request more clarity regarding the training needed to perform certain functions. For the 2 cases mentioned here, we suggest the reviewer should be a qualified physician with adequate knowledge of relevant federal regulations and guidances.
VII, F page 19	M	In the case of recovery of umbilical cords, "aseptic recovery" may not be possible.	We recommend changing wording in bullet #1 as follows: • the facility offers a suitable size, location, and is constructed so that**,** *where appropriate***,** an aseptic recovery can be successfully performed;

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
XI, B pages 27 & 28	M	The term "ancillary reagents", as defined in USP 1043 and used by the FDA, should be mentioned here.	Please refer to ancillary reagents as defined in USP 1043.
XII page 29	E	The option of 'further manufacturing' should be included.	We recommend modifying the wording in the first sentence as follows: Recovery means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion transfer *or further manufacturing*.
XIII, A page 32	E	A bullet should be included to address expansion/ manufacturing of cells	Recommend adding the following additional bullet: • Expansion of cells

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
XIII, D page 35	M	The strategy behind acceptance criteria for microbiological cultures is not clear. Specifically, <u>any</u> pre-processing cultures of *Clostridium* or *Streptococcus pyogenes* makes the HCT/P unacceptable, yet <u>multiple</u> cultures of "enteric or pathogenic" organisms are required to be unacceptable. It is open to conjecture as to how many previous cultures of the latter organisms are acceptable.	We request that this section state a rationale for why previous cultures of some organisms are acceptable while others are not, and quantify "multiple". In we request that the document indicate whether these recommendations are specific to HCT/Ps of musculoskeletal origin or are generalized to HCT/Ps from all organs.
XV page 37	C	If the November 2008 FDA Draft Guidance entitled "Process Validation: General Principles and Practices" applies to cell therapy, then this section should make reference to that guidance.	Please reference the FDA Draft Guidance on Process Validation, if it is applicable.

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
XVIII, I page 46	C	We disagree that packaging and shipping 'are not required to be validated or verified.' Furthermore, it is also recommended that shipping containers must be capable of maintaining temperature (XVIII, J) and physically protect the contents (XVIII, I).	We recommend modifying the answer as follows: Process validation or verification only applies to processing (§§ 1271.3(ff) and 1271.230(a)). The packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination (§1271.265(d)). *Where appropriate, shipping containers and shipping should be qualified or verified.*
XVIII, J page 46	E	It is not clear which industry standards are being referenced here.	Please clarify what is meant by 'industry standards'.

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
XX, C page 50	C	As part of the tracking requirements manufacturers are being asked to: 1. Inform the consignee of their internal tracking systems 2. Create a form for each product distributed, to be used by the consignee to document what was done with the product However, requirements for tracking should not be more stringent that those for the Blood Industry, where neither of these items are required. The complaint section of this draft guidance provides steps that a manufacturer must take to receive/provide information regarding possible contamination/transmission of communicable diseases, and these steps would appear to satisfy the intent of the tracking requirements listed in this section.	We recommend modifying paragraph 2 as follows: *All consignees should be registered to handle these products and comply with HCT/P regulations. Each consignee is required to have its own internal tracking system.*

Citation Location Section/Page	**Relative Impact**	**Specific Concern** (short explanation)	**Proposed Change** (additions shown in *italics*)
XXII, A page 52 & 53	M	The description of the reporting process is vague. Specifically, it should be emphasized in example 3 that the determination of causality -- whether the fever is a manifestation of an infection (which may be reportable) or another biological response (e.g., immunogenic, which may not be reportable) -- should be determined by the treating physician.	We recommend modifying the last sentence in example 3 and adding a reference to appropriate guidance as follows: "You would not be required to report this adverse reaction because there is not a reasonable possibility that the HCT/P caused the response. *For supplemental information, see "Guidance for Industry, MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 2)."*