Guidance for Industry and FDA Staff:

Minimal Manipulation of Structural Tissue Jurisdictional Update

For questions regarding this document, contact:
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U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products
and
Center for Biologics Evaluation and Research
September 2006

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Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. PURPOSE

This guidance is intended to improve the transparency of FDA's jurisdictional determinations by providing additional information about the classification and assignment of a certain class of products. The jurisdictional information contained in this guidance document may be based on a past decision made in response to a Request for Designation (RFD) submitted pursuant to 21 CFR Part 3, or in response to a request for an informal jurisdictional determination. FDA's Office of Combination Products (OCP) issues jurisdictional updates on selected classes of products on an ongoing basis. OCP selects product classes to be the subject of jurisdictional updates based on its perception of the current level of interest in the jurisdictional issue, the extent to which the class of products can be clearly described, the extent to which the existence and description of the class of products has been made public, and related factors.

This guidance document provides information about the classification of products as human cells, tissues and cellular and tissue-based product (HCT/P's) regulated solely under section 361 of the Public Health Service Act (PHS Act). Specifically, this guidance document discusses FDA's current thinking on the meaning of the phrase "minimally manipulated" contained in 21 CFR 1271.10(a)(1), and defined ("minimal manipulation") at 21 CFR 1271.3(f), as it applies to structural tissue. OCP and the Center for Biologics Evaluation and Research are jointly issuing this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. JURISDICTIONAL INFORMATION

FDA's regulations set forth the criteria that must be met for an HCT/P to be regulated solely under section 361 of the PHS Act. These criteria are that the HCT/P must:

- be minimally manipulated;
- be intended for homologous use only, as reflected in the labeling, advertising, or other indications of the manufacturer's objective intent;
- not be combined with a drug or device, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of the water, crystalloids, or sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
- not have a systemic effect and not be dependent on the metabolic activity of living cells for its primary function except if for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use.[1]

FDA regulations further define "minimal manipulation" for structural tissue as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."[2]

FDA has received several RFD's requesting a determination of whether or not certain HCT/P's will be regulated solely under section 361 of the PHS Act based on the manipulation the product undergoes during processing.[3] For purposes of determining whether a structural tissue product is minimally manipulated, a tissue characteristic is "original" if it is present in the tissue in the donor. A tissue characteristic is "relevant" if it could have a meaningful bearing on how the tissue performs when utilized for reconstruction, repair, or replacement. A characteristic of structural tissue would be relevant when it could potentially increase or decrease the utility of the original tissue for reconstruction, repair or replacement.

Accordingly, FDA's determination of whether structural tissue is eligible for regulation solely under section 361 of the PHS Act has encompassed a consideration of all the potential effects, both positive and negative, of the alteration of a particular characteristic on the utility of the tissue for reconstruction, repair or replacement, i.e., changing the

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[1] 21 CFR 1271.10(a).

[2] 21 CFR 1271.3(f)(1). For cells or nonstructural tissue, minimal manipulation is processing that does not alter the relevant biological characteristics of cells or tissues. 21 CFR 1271.3(f)(2).

[3] FDA has formed a committee known as the Tissue Reference Group (TRG) consisting of representatives from the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Office of Chief Counsel, and the Office of Combination Products to make initial recommendations on several issues pertaining to HCT/P's, including whether the product may be regulated solely under section 361 of the PHS Act. TRG recommendations may be appealed through the Request for Designation process, as outlined in 21 CFR Part 3. Further information about the TRG may be found at http://www.fda.gov/cber/tissue/tisrefgrp.htm.

characteristic could improve or diminish the tissue's utility. Once FDA has determined, based on the data and information before it, that processing has altered an original characteristic of a structural tissue, and that the characteristic is relevant in that it has a potential effect on the utility of the tissue for reconstruction, repair, or replacement, the agency has considered the tissue to be more than minimally manipulated and not eligible for regulation solely under section 361 of the PHS Act.[4] In such a case the structural tissue will be regulated as a drug, device and/or biological product under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the PHS Act.[5]

III. FOR FURTHER INFORMATION

For an initial determination whether a particular HCT/P will be regulated solely under section 361 or regulated as a drug, device or biological product, contact:

Office of Cellular, Tissue and Gene Therapies
Tissue Reference Group[6]
Telephone: 301-827-6176

The Office of Combination Products may also be contacted at

Suite 200, HFG-3
15800 Crabbs Branch Way
Rockville, Maryland 20855
Telephone: 301-427-1934
e-mail: combination@fda.gov

A formal determination of the classification or assignment of a particular product may be made through the Request for Designation (RFD) process. Further information about the RFD process is available at 21 CFR Part 3, www.fda.gov/oc/ombudsman/part3&5.htm and in the document "Guidance for Industry and FDA: How to Write a Request for Designation (RFD)," available at www.fda.gov/oc/combination/. We recommend that sponsors call OCP at 301-427-1934 to discuss their particular situation before submitting an RFD.

OCP is always available as a resource to you. We encourage you to contact OCP if you have any questions about the jurisdiction of your product.

[4] 21 CFR 1271.10
[5] 21 CFR 1271.20
[6] Further information about FDA's regulation of HCT/P's and the Tissue Reference Group may be found at http://www.fda.gov/cber/tiss.htm.