

FDA's Regulatory Scheme for Human Tissue

A Brief Overview

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In recent years, industry has accelerated the development of novel cellular and tissue-based products that provide increasingly useful therapies for a wide range of medical conditions. The Food and Drug Administration (FDA) calls these products “human cells, tissues, and cellular or tissue-based products” (HCT/Ps). With relatively little fanfare, the agency has adapted to this development by promulgating through notice and comment rulemaking a new regulatory scheme to address the key disease transmission concerns raised by these products. These regulations, set forth in 21 C.F.R. Part 1271, are based upon the statutory authority to prevent the spread of communicable disease granted to FDA in Section 361 of the Public Health Service Act (PHS Act).¹ As discussed below, some HCT/Ps are eligible for regulation solely under Part 1271. Other HCT/Ps are regulated under both Part 1271 and FDA's traditional premarket and post-

market regulation of medical devices and drugs under the Federal Food, Drug, and Cosmetic Act (FDCA), and biological products under section 351 of the PHS Act.

This article explains the jurisdictional criteria for regulation of a product as an HCT/P solely under Part 1271. The article also describes the process for requesting an informal jurisdictional determination on this question from the Tissue Reference Group (TRG), as well as the Request for Designation (RFD) process for requesting a formal determination from the Office of Combination Products (OCP).

What Are HCT/Ps?

FDA defines HCT/Ps as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”² Examples of such products include “bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progeni-



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tor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.”³

FDA expressly excludes the following from regulation as HCT/Ps: vascularized human organs for transplantation; whole blood or blood components or derivative products already regulated as biologics under 21 C.F.R. Parts 607 and 207; secreted or extracted human products except semen (e.g., milk collagen, and cell factors); minimally manipulated bone marrow for homologous use (and not combined with another article except for water, crystalloids, or a sterilizing, preserving, or storage agent that does not raise new clinical safety concerns with respect to the HCT/P); ancillary products used in the manufacture of an HCT/P; cells, tissues and organs derived from animals other than humans; and in vitro diagnostic products.⁴

Overlapping Regulatory Schemes

In 21 C.F.R. Part 1271, FDA sets forth the regulatory scheme for HCT/Ps. The basic authority FDA has relied upon is section 361 of the PHS Act, which authorizes FDA to “make and enforce such regulations as ... are necessary to prevent the introduction, transmission, or spread of communicable diseases.” This provision was also the authority for 21 C.F.R. Part 1270, which was the basic regulation governing human tissue products for more than a decade. The superseding regulations in Part 1271 apply only to HCT/Ps recovered on or after May 25, 2005. Part 1270 will be revoked when FDA has determined that no more tissue recovered prior to that date is available for distribution.

In Part 1271, FDA sets forth requirements for: 1) registration and listing; 2) donor screening and testing; 3) CGTPs; 4) labeling; 5) adverse-event reporting; and 6) inspection and enforcement. An HCT/P that meets the Part 1271 criteria for regulation solely under section 361 of the PHS Act and the regulations in Part 1271 is called a “361 HCT/P.” Such products are not subject to any premarket review requirements. The Center for Biologics Evaluation and Research (CBER) has jurisdiction over 361 HCT/Ps.

An HCT/P that is subject to Part 1271 but does not meet the criteria for regulation as a 361 HCT/P may be subject to an additional layer of regulation as a drug, medical device or biological product. HCT/Ps that meet the definition of a drug or device are regulated under the traditional premarket and postmarket requirements arising under the FDCA. For example, device HCT/Ps must receive 510(k) clearance or premarket approval (PMA), and drug HCT/Ps must receive new drug application (NDA) approval. Device HCT/Ps must comply with the Quality System regulation (QSR)⁵ and drug HCT/Ps must comply with current good manufacturing practice (CGMPs) regulations.⁶ The Center for Drug Evaluation and Research (CDER) is responsible for regulating drug HCT/Ps, and the Center for Devices and Radiological Health (CDRH) is responsible for device HCT/Ps.

HCT/Ps that meet the definition of a biological product are subject to traditional premarket and postmarket requirements arising under section 351 of the PHS Act. These “351 HCT/Ps” require approval of a biologic license application (BLA),⁷ and their manufacture must comply with CGMPs.

CBER is responsible for regulating 351 HCT/Ps.

Criteria for 361 HCT/Ps

A product eligible for regulation as a 361 HCT/P solely under Part 1271 is not subject to premarket clearance or approval. To be a 361 HCT/P, the product must meet all four of the following criteria:

- It is minimally manipulated.
- It is intended for homologous use as determined by labeling and advertising.
- Its manufacture does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for the HCT/P).
- It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, it is intended for autologous use or allogeneic use in close relatives or for reproductive use. (FDA has postponed the application of most Part 1271 requirements with respect to reproductive tissue.)⁸

The definition of “minimal manipulation” depends upon whether the HCT/P is a structural tissue, as opposed to cells or nonstructural tissue. For structural tissue, FDA defines “minimal manipulation” as “processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.”⁹ FDA’s guidance explains that a tissue characteristic is “original” if it is present in the donor’s tissue.¹⁰ A tissue characteristic is “relevant” if it could have a meaningful bearing on how the tissue performs when utilized for reconstruction, repair or replacement.¹¹ If FDA determines that processing has

altered an original characteristic of a structural tissue and that the characteristic would have a potential effect on the tissue's utility, the tissue is deemed more than minimally manipulated and not eligible for regulation solely under section 361 of the PHS Act.¹² FDA has stated that cutting, grinding, shaping, soaking in antibiotic solution, sterilization by gamma irradiation, lyophilization, freezing, and demineralization of bone are all examples of minimal manipulation.¹³

For cells or nonstructural tissue, "minimal manipulation" means "processing that does not alter the relevant biological characteristics of cells or tissues."¹⁴ FDA has stated that density-gradient separation, cell selection, centrifugation, and cryopreservation constitute minimal manipulation.¹⁵ In contrast, the agency has concluded that cell expansion in culture and human skin processed into human collagen are examples of more than minimal manipulation.¹⁶

The term "homologous use" is defined as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."¹⁷ FDA recognizes that homologous use does not require that tissue be used in its native location or even an analogous location.¹⁸ In determining whether a product is intended for homologous use, FDA considers the manufacturer's objective intent, as manifested in the product's advertising and labeling. In the agency's view, the homologous-use criterion protects against "promotion of an HCT/P for an unproven therapeutic use, such as curing cancer."¹⁹ Therefore, FDA considers the nonhomologous use criterion "to be

a meaningful indicator" that regulation of the product as a 361 HCT/P would not be appropriate.²⁰

FDA has stated that it intends to "interpret 'nonhomologous' narrowly."²¹ FDA has stated that nonhomologous uses include: using dermis as a replacement for dura mater (which encapsulates the brain); the use of amniotic membrane in the eye; and use of cartilage in the bladder.²²

Deciding Whether To Consult FDA

Manufacturers and sponsors are permitted to self-determine whether their HCT/Ps are 361 HCT/Ps. Thus, manufacturers must choose whether to simply place their product on the market or to seek advice from FDA prior to marketing as to whether their particular product is eligible for regulation as a 361 HCT/P. On the one hand, it is faster and less burdensome to simply proceed to market. On the other hand, if the product is placed on the market and FDA later objects, the manufacturer may be faced with the unpleasant prospect of enforcement sanctions and the necessity of withdrawing the product from the market.

One important element of this decision is assessing how well the product fits within the Section 361 criteria. In some cases, the answer will be fairly obvious one way or the other. In other cases, the answer may be unclear. FDA's definition of a 361 HCT/P has a fair degree of subjectiveness, particularly with respect to whether a product has been minimally manipulated or is intended for homologous use. This leaves room for a manufacturer to exercise creativity in applying these definitions to its product, but in some circumstances the prudent course is to seek FDA's advice before going to market.

Obtaining FDA's Views

In 1997, FDA formed a committee known as the Tissue Reference Group (TRG). It is intended to provide a single reference point for product-specific questions received by the Centers or the OCP concerning jurisdiction and applicable regulation of HCT/Ps. The types of questions the TRG considers include whether a particular HCT/P meets the criteria for regulation solely under section 361 of the PHS Act; is a drug, device, or biologic; and what the primary mode of action of a combination product is.

The TRG is composed of representatives of CBER, CDER, the Office of Chief Counsel, and the OCP. It meets twice a month to consider these questions and make initial recommendations. The TRG procedures are described in Standard Operating Procedures and Policies 8004 (SOPP 8004). Manufacturers send their inquiry concerning regulation of an HCT/P to the executive secretary of the TRG. A wise manufacturer will include a clear product description and will proactively explain why it meets the definition of a 361 HCT/P under FDA's regulations.

The executive secretary places such inquiries, along with accompanying information about the product, on the agenda for the next scheduled TRG meeting. The TRG attempts to respond in writing within sixty days of receiving an inquiry. If the TRG determines that there is insufficient information, the executive secretary will communicate this to the manufacturer, and the TRG will consider any additional information at the next available meeting after receipt. A manufacturer may ask to meet with the TRG to present information.

In some cases, the TRG initiates contact with a manufacturer to ask why

it believes that a marketed product is a Section 361 HCT/P. If contacted, the manufacturer should likewise provide a clear product description and proactive explanation as to why the criteria for a Section 361 HCT/P are met.

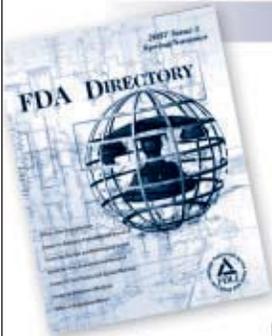
When the TRG makes a determination, the executive secretary prepares a draft response letter and circulates it by email for TRG review. The letter is then forwarded to CBER's Senior Policy Advisor and Counselor for Biologics, and to the Center Directors of CBER and CDRH for review and signature, and the signed letter is returned to the executive secretary for mailing to the manufacturer. A manufacturer may appeal the recommendation through the RFD process, pursuant to 21 C.F.R. Part 3.²³ For a more formal determination of HCT/P jurisdiction, a manufacturer or sponsor may go directly to the OCP by

filing an RFD, which will be sent to the Centers' product jurisdiction officers and to the TRG where appropriate.

A Final Word: Revising Claims

If FDA takes the position that a product does not meet the requirements for a Section 361 HCT/P, that is not necessarily the last word. Often, FDA's determination is dependent upon the nature of the claims being made for a product. For example, claims of active biologic activity may lead FDA to conclude that the use is non-homologous, and a revision of the claims may lead FDA to agree that Section 361 status now applies. Therefore, a manufacturer from the outset should be very careful about the precise claims made for a Section 361 HCT/P and should be willing to consider revisions if FDA believes that Section 361 status may not apply. Δ

1 42 U.S.C. § 264.
 2 21 C.F.R. § 1271.3(d).
 3 *Id.*
 4 *Id.*
 5 21 C.F.R. Part 820.
 6 21 C.F.R. Parts 210 and 211.
 7 42 U.S.C. § 262.
 8 21 C.F.R. § 1271.10(a).
 9 21 C.F.R. § 1271.3(f)(1).
 10 FDA, "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update," at 2 (Sept. 2006), available at www.fda.gov/oc/combination/manipulation.html.
 11 *Id.*
 12 *Id.* at 3.
 13 63 Fed. Reg. 26,744, 26,748-49 (May 14, 1998).
 14 21 C.F.R. § 1271.3(f)(2).
 15 63 Fed. Reg. at 26,748; 66 Fed. Reg. 5447, 5457 (Jan. 19, 2001).
 16 63 Fed. Reg. at 26,748.
 17 21 C.F.R. § 1271.3(c).
 18 66 Fed. Reg. at 5478.
 19 *Id.* at 5458.
 20 *Id.*
 21 *Id.*
 22 *Id.*
 23 See FDA, "Guidance for Industry and FDA: How to Write a Request for Designation (RFD)" (Aug. 2005), available at www.fda.gov/oc/combination/howtowrite.html.



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