Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products in the Office of the Commissioner (OCP)
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Draft Guidance for Industry

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA or Agency's) current thinking on this topic.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 appropriate 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. INTRODUCTION

FDA defines articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient as "human cells, tissues, or cellular or tissue-based products" (HCT/Ps) in Title 21 of the Code of the Federal Regulations (CFR) Part 1271, specifically 21 CFR 1271.3(d). The Agency regulates HCT/Ps with a tiered, risk-based approach designed to provide the appropriate level of oversight to protect the public health. We, FDA, are issuing this guidance to provide you, sponsors, clinicians, and other establishments that manufacture[1] and use HCT/Ps from adipose tissue, with recommendations for complying with the regulatory requirements for HCT/Ps, as set forth in 21 CFR Part 1271, as established under the authority of section 361 of the Public Health Service (PHS) Act as well as recommendations for complying with section 351 of the PHS Act and the Federal Food, Drug, and Cosmetic (FD&C) Act, and the applicable regulations.

HCT/Ps include adipose tissue and cells obtained from adipose tissue. Adipose tissue is typically defined as a connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs. It is composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa.[2] Additionally, adipose tissue

[1] The term "manufacture" means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor (21 CFR 1271.3(e)).

[2] Chapter 6. Adipose Tissue. In: Mescher AL. eds. *Junqueira's Basic Histology: Text & Atlas, 13e.* New York: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=574&Sectionid=42524592.

contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and a variety of immune cells.[3] Because connective tissue provides structure and support to the body, FDA considers connective tissue, including adipose tissue, to be a structural tissue.

FDA has recently received numerous inquiries regarding HCT/Ps manufactured from adipose tissues. This guidance, when finalized, will provide the Agency's current thinking with respect to regulatory considerations for adipose tissue.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Under FDA's risk-based HCT/P regulatory framework, which is set forth in 21 CFR Part 1271, certain HCT/Ps are regulated solely under section 361 of the PHS Act and the regulations under 21 CFR Part 1271; no premarket review is required for these HCT/Ps. In 21 CFR 1271.10, the regulations identify the criteria for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria (21 CFR 1271.10(a)):

1) The HCT/P is minimally manipulated;
2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4) Either:
    i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a) Is for autologous use;
        b) Is for allogeneic use in a first-degree or second-degree blood relative; or
        c) Is for reproductive use.

[3] Brown SA, Levi, B, Lequeux, C, et al. Basic Science Review on Adipose Tissue for Clinicians. *Plast. Reconstr. Surg.* 126:1936, 2010

III. IS MY HCT/P FROM ADIPOSE TISSUE REGULATED AS A DRUG, DEVICE, AND/OR BIOLOGICAL PRODUCT?

An HCT/P that does not meet all of the criteria set out in 21 CFR 1271.10(a), and the establishment that manufactures the HCT/P does not qualify for any of the exceptions in 21 CFR 1271.15, will be regulated as a drug, device, and/or biological product under the FD&C Act and/or section 351 of the PHS Act, and the applicable regulations. This section of the guidance describes FDA's current thinking as to how the four criteria in 21 CFR 1271.10(a) apply to HCT/Ps from adipose tissue and provides relevant examples of HCT/Ps from adipose tissue as well as the appropriate regulatory pathway with respect to each example. In some of the examples, the HCT/Ps from adipose tissue may fail to meet more than one of the four criteria in 21 CFR 1271.10(a). In addition, this section identifies certain regulations that apply if an HCT/P from adipose tissue is regulated as a drug, device, and/or biological product. This section also describes the requirements applicable to you as a manufacturer of an HCT/P from adipose tissue that meets the criteria for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271.

A. Is My HCT/P from Adipose Tissue More Than Minimally Manipulated? 21 CFR 1271.10(a)(1)

Under the 21 CFR Part 1271 regulatory framework, a structural tissue is more than minimally manipulated if the processing alters the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement (21 CFR 1271.3(f)(1)). As described above, adipose tissue is typically defined as a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed with small blood vessels, divided into lobes and lobules by connective tissue septa.

For purposes of applying the regulatory framework, we generally consider adipose tissue to be a structural tissue, with characteristics for reconstruction, repair, or replacement that relate to its utility to cushion and support the other tissues in the subcutaneous layer (subcutaneum) and skin.

Adipose tissue is sometimes processed by various means (e.g., enzymatic digestion, mechanical disruption, etc.) to isolate the non-adipocyte or non-structural components of adipose tissue. In some instances, these non-adipocyte or non-structural components are cultured and expanded. Processing to isolate non-adipocyte or non-structural components from adipose tissue (with or without subsequent cell culture or expansion) is generally considered more than minimal manipulation. This is because the connective tissue and structural components of the adipose tissue are entirely removed from the non-adipocyte or non-structural isolates, thereby altering the original relevant characteristics relating to the tissue's utility for reconstruction, repair, or replacement.

Adipose tissue may also be processed to remove cellular components to obtain the decellularized extracellular matrix portion of adipose tissue. Adipose tissue processed this way generally is considered more than minimally manipulated because removal of the cells leaves very little bulk and alters the ability of the adipose tissue to provide cushioning and support.

In contrast, processing that does not affect the adipose tissue's utility as a structural tissue for reconstruction, replacement, or repair may be considered minimal manipulation. Examples include aliquoting, rinsing, removal of macroscopic debris, and freezing.

Example A-1: Adipose tissue is recovered by tumescent liposuction. The adipose tissue undergoes processing or manipulation (e.g., enzymatic digestion, mechanical disruption, etc.) to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells for clinical therapeutic uses. This processing breaks down and eliminates the structural components that function to provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement. Therefore, based on the definition of minimal manipulation for structural tissue, this processing would generally be considered more than minimal manipulation.

Example A-2: Adipose tissue is recovered from a deceased donor and is treated with acid and/or detergent, washed, de-cellularized, and ground to obtain a homogenous fibrous tissue suspension. This processing to remove adipocytes and manufacture an acellular adipose tissue matrix or scaffold alters the original relevant characteristics of the adipose tissue relating to its ability to cushion and support the subcutaneum. Therefore, this processing would generally be considered more than minimal manipulation.

B. What is Homologous Use of My HCT/P from Adipose Tissue? 21 CFR 1271.10(a)(2)

The use of the HCT/P from adipose tissue is determined from the labeling, advertising, or other indications of the manufacturer's objective intent. To evaluate whether the use of an adipose derived HCT/P would meet the regulatory definition of homologous use, you should consider whether the adipose tissue used for the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues performs the same basic function or functions[4] in the recipient as in the donor (21 CFR 1271.3(c)).

[4] When the Agency initially proposed this exception, FDA explained that basic function of a structural tissue is what the tissue does from a biological/physiological point of view, or is capable of doing when in its original state. See "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue Based Products, 63 *Federal Register* 26744 at 26749 (May 14, 1998).

For example, the use of an HCT/P from adipose tissue for the repair, reconstruction, replacement, or supplementation of a subcutaneous adipose tissue defect would be considered a homologous use (21 CFR 1271.10(a)(2)). In these situations, FDA would consider the HCT/P from adipose tissue to be performing the same basic function in the recipient as in the donor (21 CFR 1271.3(c)).

Example B-1: Adipose tissue is recovered and processed for use, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, to cosmetically fill voids in the subcutaneous space in the face or hands. Because this use is a basic function of adipose tissue, to support the subcutaneum, using HCT/Ps from adipose tissues in this manner would generally be considered a homologous use.

Example B-2: Adipose tissue is recovered and processed for use, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, to treat bone and joint disease. Because adipose tissue does not perform this function in the donor, using HCT/Ps from adipose tissue to treat bone and joint disease is generally considered a non-homologous use.

Example B-3: Adipose tissue is recovered and processed for injection into the breast, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, for non-implant breast augmentation. The breast is composed of lobes of glandular tissue and branching ducts, interspersed with fat and ligaments that support the breast and give it shape; and nerves, blood vessels, and lymphatic tissues. The basic function of breast tissue is to produce milk (lactation) after childbirth. Because this is not a basic function of adipose tissue, using HCT/Ps from adipose tissues for breast augmentation would generally be considered a non-homologous use.

C. What if I Combine My HCT/P from Adipose Tissue with Another Product? 21 CFR 1271.10(a)(3)

If you combine your HCT/P from adipose tissue with an article except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect the HCT/P, your HCT/P from adipose tissue would be regulated as a drug, device, and/or biological product under the FD&C Act and/or section 351 of the PHS Act, and the applicable regulations.

D. What if My HCT/P from Adipose Tissue has a Systemic Effect or is Dependent on the Metabolic Activity of a Living Cell for its Primary Function? 21 CFR 1271.10(a)(4)

If the HCT/P from adipose tissue has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is not intended for autologous use or use by a first- or second-degree blood relative, then it does not meet the criteria in

21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271. Autologous use is the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered (21 CFR 1271.3(a)).

Example D-1: Adipose tissue is recovered from an unrelated allogeneic donor. Stem cells are isolated from that adipose tissue and seeded onto a bone scaffold for repair of pathologically or surgically created bony voids. The manufacturer advertises the stem cells as contributing to the primary function of filling, augmenting, or repairing the bone void by giving rise to osteoblasts, which mineralize the allograft and increase its durability; this function depends on the metabolic activity of the cells. The HCT/P from adipose tissue is dependent upon the metabolic activity of living cells for its described primary function of repairing the bone void and it is not intended for autologous use or allogeneic use in a first- or second-degree blood relative. Therefore, the HCT/P would generally be considered not to meet the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271.

E. What Regulations Apply if My HCT/P from Adipose Tissue is Regulated as a Biological Product?[5]

HCT/Ps that are regulated as biological products, are subject to section 351 of the PHS Act and the FD&C Act, and require pre-market approval. Such HCT/Ps are subject to the applicable drug regulations, including the requirements in Parts 210 and 211, and the applicable requirements in Parts 600 through 680. Such products are also regulated under section 361 of the PHS Act and are subject to requirements in Part 1271 designed to prevent the introduction, transmission, and spread of communicable diseases. As part of these regulations, you are required to register as an establishment, and list your HCT/Ps (21 CFR 1271.1(b)(2)) (see section V.C. of this document).

In order to lawfully market a biological product, a biologics license must be in effect (42 USC 262(a)). Such licenses are issued only after a determination by FDA that the establishment(s) and the biological products meet the applicable requirements to ensure the continued safety, purity, and potency of such products (21 CFR 601.2(d)). For clinical studies of investigational drug products, the sponsor must have an investigational new drug (IND) application in effect in accordance with the FD&C Act (21 USC 355(i)) and FDA regulations (21 CFR Part 312 and 21 CFR 601.21). See section V.B. of this document about obtaining more information regarding the IND process.

[5] Some HCT/Ps from adipose tissue may be regulated as devices. For more information about device regulation, see CDRH's webpage Device Advice – Overview of Medical Device Regulation (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm). Refer to section V.A below regarding obtaining more information about the regulatory considerations of your HCT/P from adipose tissue.

F. What Must I do if My HCT/P from Adipose Tissue Meets the Criteria for Regulation Solely Under Section 361 of the PHS Act and Part 1271?

If you are a domestic or foreign establishment that manufactures an HCT/P that is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271, you must, in accordance with 21 CFR 1271.1(b)(1):

1) Register with FDA (See section V.C. of this document);
2) Submit to FDA a list of each HCT/P manufactured; and
3) Comply with all applicable requirements contained in 21 CFR Part 1271.

Establishment means a place of business under one management, at one general physical location that engages in the manufacture of HCT/Ps, including:

1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of HCT/Ps; and
2) Facilities that engage in contract manufacturing services for a manufacturer of HCT/Ps.

(21 CFR 1271.3(b)).

Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening and testing of the cell or tissue donor (21 CFR 1271.3(e)).

Example F-1: Adipose tissue is recovered by tumescent liposuction. The lipoaspirate is processed to eliminate macroscopic debris to produce a smooth and uniform suspension for subcutaneous injection to cosmetically fill voids in the subcutaneous space in the face or hand. Provided the adipose tissue meets all of the criteria in § 1271.10(a), this HCT/P from adipose tissue, processed and used in this manner, would be regulated solely under section 361 of the PHS Act and 21 CFR Part 1271. The facility that is processing the adipose tissue is manufacturing an HCT/P from adipose tissue, and is required to register with FDA and comply with all requirements in 21 CFR Part 1271 applicable to the manufacturing steps that it performs.

IV. EXCEPTIONS TO FDA REGULATION 21 CFR 1271.15

A. Is My HCT/P from Adipose Tissue that is Implanted into the Same Individual During the Same Surgical Procedure Subject to FDA Regulation? 21 CFR 1271.15(b)

Part 1271 recognizes exceptions from the requirements of 21 CFR Part 1271. Typically this would mean that products and establishments that meet one of these exceptions are not subject to FDA regulation. Under 21 CFR 1271.15(b), an establishment is not required to comply with the requirements of 21 CFR Part 1271 if it removes HCT/Ps from an

individual and implants such HCT/Ps into the same individual during the same surgical procedure. If your establishment meets this exception, you are not required to comply with the HCT/P requirements in 21 CFR Part 1271.[6]

In regard to HCT/Ps from adipose tissue, we generally consider the exception in 21 CFR 1271.15(b) to apply only if the HCT/P from adipose tissue is for autologous use, is removed and implanted within a single operation or in a limited number of predetermined operations in order to achieve the intended effect, and does not undergo processing steps beyond rinsing, cleansing, or sizing. Limited handling such as rinsing and cleansing to remove debris would allow the HCT/P from adipose tissue to retain the structural function, while other processing steps such as cell isolation, cell expansion, or enzymatic digestion generally would not. Thus, if such other processing steps are performed that prevent the HCT/P from adipose tissue from remaining "such HCT/P," the establishment manufacturing the HCT/P from adipose tissue would generally not be considered to meet the exception under 21 CFR 1271.15(b).

Example A-1: Adipose tissue is recovered by tumescent liposuction. The lipoaspirate is centrifuged at a low speed before blood and extracellular fluid are decanted. The remaining adipose tissue is resuspended in sterile saline. Because nothing else is added to the adipose tissue, and only minor handling is performed (e.g., no steps were taken to isolate stem cells from the lipoaspirate, commonly referred to as stromal vascular fraction), the adipose tissue would remain a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed small blood vessels. It is then re-injected into the subcutaneous space of the same patient from whom it was removed, in a single operation or in a limited number of predetermined operations in order to achieve the intended effect. We generally would consider the establishment manufacturing this HCT/P from adipose tissue to meet the exception under 21 CFR 1271.15(b), and the establishment would not be required to comply with the requirements in 21 CFR Part 1271.

Example A-2: Adipose tissue is recovered by tumescent liposuction. Stem cells from the lipoaspirate are then isolated. Cell isolation would typically cause the adipose tissue to no longer be "such HCT/P." Thus, even if this processed HCT/P from adipose tissue is injected into the same patient from whom it was removed during the same surgical procedure, the establishment would generally not be considered to qualify for the exception under 21 CFR 1271.15(b).

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[6] For more information on this topic, you may wish to consult the draft guidance entitled, "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Draft Guidance for Industry" dated October 2014. When finalized, this guidance will represent FDA's current thinking on this topic.

B. Are There Other Exceptions that Would Result in Me or My HCT/P from Adipose Tissue Being Excepted from FDA Regulation?

Yes, there are additional exceptions described in 21 CFR 1271.15. If you meet any one of the following exceptions, you are not required to comply with the regulations in 21 CFR Part 1271:

1) You are an establishment that uses HCT/Ps solely for nonclinical scientific or educational purposes (21 CFR 1271.15(a)).

2) You are a carrier who accepts, receives, carries, or delivers HCT/Ps in the usual course of business as a carrier (21 CFR 1271.15(c)).

3) You are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within your facility (21 CFR 1271.15(d)).

4) You are not required to register or list your HCT/Ps independently, but you must comply with all other applicable requirements in Part 1271, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment (21 CFR 1271.15(f)).

C. What Must I Do if I Do Not Meet One of the Exceptions Listed in 21 CFR 1271.15?

If you are an establishment that manufactures an HCT/P and you do not qualify for any of the exceptions under 21 CFR 1271.15, your HCT/P from adipose tissue will be regulated as a drug, device, and/or biological product unless, as previously described, it meets all of the criteria in 21 CFR 1271.10. If your HCT/P is regulated as a drug, device, and/or biological product it will be subject to the FD&C Act and/or section 351 of the PHS Act, and the applicable regulations in 21 CFR Part 1271 as well as 21 CFR Parts 210, 211, 600 through 680, and 820 through 821. If your HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271, you must comply with all requirements in 21 CFR Part 1271 applicable to the manufacturing steps you perform.

V. ADDITIONAL INFORMATION

A. How Can I Get More Information About the Appropriate Regulatory Considerations for My HCT/P from Adipose Tissue?

The Agency provides two mechanisms through which a manufacturer may obtain a recommendation or decision regarding the classification of an HCT/P:

1) The Tissue Reference Group, a group comprised of representatives from CBER and the Center for Devices and Radiological Health (CDRH), provides product sponsors with an informal process through which they may obtain an Agency recommendation regarding the application of the criteria in 21 CFR 1271.10(a) to their HCT/Ps for a given indication. Information about this process as well as what you may want to include to facilitate review of your request can be found at: http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm

2) A Request for Designation (RFD) may be submitted to the Office of Combination Products (OCP) to obtain a formal Agency decision regarding the regulatory identity or classification of an HCT/P (21 CFR Part 3). A description of that process and information on how to submit an RFD can be found at: http://www.fda.gov/CombinationProducts/RFDProcess/default.htm. Additional information may be found at http://www.fda.gov/Regulatoryinformation/Guidances/ucm126053.htm. You may also contact OCP to obtain an informal classification for your HCT/P.

You may use either one of these mechanisms to obtain a response to a question as to whether your adipose tissue-derived HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271, or if it meets one of the exceptions in 21 CFR 1271.15.

B. How Can I Get More Information About the IND Process for My HCT/P from Adipose Tissue that Requires Premarket Approval?

Further information about IND requirements for biological products may be obtained through the Regulatory Management Staff, Office of Cellular, Tissue, and Gene Therapies, at 240-402-8190 or CBEROCTGTRMS@fda.hhs.gov.

C. How Do I Register as an HCT/P Manufacturer?

FDA regulations require establishments that perform one or more steps in the manufacture of HCT/Ps to register and submit a list the products with the Agency. If you are a manufacturer that is required to register, you must do so within 5 days after beginning operations (21 CFR 1271.21(a)). Registrations must be updated annually in December, except if the ownership or location of the establishment changes, you must submit an amendment to the registration within five days of the change (21 CFR 1271.21(b)).

FDA has created Form FDA-3356, Establishment Registration and Listing for HCT/Ps, for establishments to submit HCT/P establishment registration and listing information to FDA. The form can be submitted electronically, (Electronic Human Cell and Tissue Establishment Registration (eHCTERs). Instructions for completing the electronic registration form are located on our website, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/ucm148775.htm.

Form FDA-3356 may also be completed and submitted by mail. Questions about HCT/P registration can be directed to: tissuereg@fda.hhs.gov.