

# **Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use**

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## **Guidance for Industry and Food and Drug Administration Staff**

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Center for Devices and Radiological Health  
Office of Combination Products  
November 2017**

# Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

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# Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

## Guidance for Industry and Food and Drug Administration Staff

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### I. INTRODUCTION

We, FDA, are providing you, human cells, tissues, and cellular and tissue-based product (HCT/P) manufacturers, healthcare providers, and FDA staff, with our current thinking on the criteria under Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically the 21 CFR 1271.10(a)(1) criterion of minimal manipulation and the 21 CFR 1271.10(a)(2) criterion of homologous use. The interpretation of the minimal manipulation and homologous use criteria and definitions of related key terms have been of considerable interest to industry stakeholders since the criteria and definitions were first proposed.<sup>1</sup> This guidance is intended to improve stakeholders' understanding of the definitions of minimal manipulation in 21 CFR 1271.3(f) and homologous use in 21 CFR 1271.3(c). It will also facilitate stakeholders' understanding of how the regulatory criteria in 21 CFR 1271.10(a)(1) and (2) apply to their HCT/Ps.<sup>2</sup> In addition, we are informing manufacturers, healthcare providers, and other interested persons that over the next 36 months, we intend to exercise enforcement discretion under limited conditions with respect to the investigational new drug (IND) application and premarket approval (biologics license application (BLA)) requirements, for certain HCT/Ps.

This guidance finalizes the document entitled "Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and Food Administration Staff" dated December 2014, and "Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and FDA Staff" dated October 2015. This guidance also finalizes certain material related to adipose tissue that was included in draft guidance entitled "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for

<sup>1</sup> "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26748-26749 (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

<sup>2</sup> This guidance does not address the classification and/or assignment of HCT/Ps that do not meet the criteria for regulation solely under section 361 of the Public Health Service (PHS) Act and 21 CFR Part 1271.

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Industry” dated December 2014 (Adipose Draft Guidance). This material, together with the material related to adipose tissue included in the final guidance entitled “Same Surgical Procedure Exception under 21 CFR 1271.15(b); Questions and Answers Regarding the Scope of the Exception” dated November 2017, supersedes the Adipose Draft Guidance. Accordingly, we do not intend to finalize the Adipose Draft Guidance, which is now withdrawn. Finally, this guidance supersedes the document entitled “Minimal Manipulation of Structural Tissue (Jurisdictional Update); Guidance for Industry and FDA Staff” dated September 2006 (2006 Guidance).

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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

HCT/Ps are defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.<sup>3</sup> Because of the unique nature of HCT/Ps, FDA proposed and in 2005 implemented a tiered, risk-based approach to the regulation of HCT/Ps. Although FDA is authorized to apply the requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) to those products that meet the definition of drug, biologic, or device, under this tiered, risk-based approach, those HCT/Ps that meet specific criteria or fall within detailed exceptions do not require premarket review and approval. In developing the tiered, risk-based approach the agency focused on public health and regulatory concerns, including how transmission of communicable disease can be prevented; what processing controls are necessary to prevent contamination that could result in an unsafe or ineffective product, and to preserve integrity and function so that the products will work as they are intended; and how clinical safety and effectiveness can be assured. The tiered, risk-based approach is contained in a set of regulations commonly referred to as the “tissue rules,” issued by FDA through notice and comment rulemaking, under the communicable disease authority of section 361 of the PHS Act

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<sup>3</sup> Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps: (1) Vascularized human organs for transplantation; (2) Whole Blood or blood components or blood derivative products subject to listing under 21 CFR Parts 607 and 207, respectively; (3) Secreted or extracted human products, such as milk, collagen, and cell factors, except that semen is considered an HCT/P; (4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); (5) Ancillary products used in the manufacture of HCT/P; (6) Cells, tissues, and organs derived from animals other than humans; (7) In vitro diagnostic products as defined in 21 CFR 809.3(a); and (8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2 that are intended for use in organ transplantation and labeled “For use in organ transplantation only.” (21 CFR 1271.3(d))

Please note, the regulatory status of products identified as not being HCT/Ps is beyond the scope of this guidance.

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(42 U.S.C. 264). These regulations explain the types of HCT/Ps that do not require premarket approval; and the registration, manufacturing, and reporting steps that must be taken to prevent the introduction, transmission, and spread of communicable disease by these HCT/Ps. These regulations can be found in 21 CFR Part 1271<sup>4</sup>.

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.

If an HCT/P does not meet 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<sup>5</sup>, the HCT/P will be regulated as a drug, device, and/or biological product under the FD&C Act, and/or section 351 of the PHS Act (42 U.S.C. 262), and applicable regulations, including 21 CFR Part 1271, and premarket review will be required.

### **Minimal Manipulation**

Section 1271.10(a)(1) (21 CFR 1271.10(a)(1)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in Part 1271 is that the HCT/P is minimally manipulated. As defined in 21 CFR 1271.3(f), minimal manipulation means:

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<sup>4</sup> See "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing;" Final Rule, 66 FR 5447 (January 19, 2001); "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products;" Final Rule, 69 FR 29786 (May 25, 2004); "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement;" Final Rule, 69 FR 68612 (November 24, 2004).

<sup>5</sup> See the "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry" dated November 2017 available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf>

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- 1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
- 2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

FDA discussed these terms in the preamble to the HCT/P Establishment Registration and Listing final rule<sup>6</sup> and the 2006 Guidance. However, we have received requests from stakeholders to provide additional guidance that explains our current thinking related to meeting the criterion in 21 CFR 1271.10(a)(1). This guidance supersedes the 2006 Guidance.

Please note that if information does not exist to show that the processing meets the definition of minimal manipulation, FDA considers the processing of an HCT/P to be “more than minimal manipulation” that cannot qualify for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271.<sup>7</sup>

### **Homologous Use**

Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in Part 1271 is that the “HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent.” As defined in 21 CFR 1271.3(c), homologous use means 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. This criterion reflects the Agency's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior, whereas HCT/Ps for homologous use can reasonably be expected to function appropriately (assuming all of the other criteria are also met)<sup>8</sup>.

In applying the homologous use criterion, FDA will determine what the intended use of the HCT/P is, as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent, and will then apply the homologous use definition.

FDA has received many inquiries from manufacturers about whether their HCT/Ps meet the minimal manipulation and/or homologous use criteria. Additionally, transplant and healthcare providers often need to know this information about the HCT/Ps that they are considering for use in their patients. This guidance provides examples of different types of HCT/Ps and how the regulations in 21 CFR 1271.10(a)(1) and (2) apply to them, and provides general principles that can be applied to HCT/Ps that may be developed in the future. In some of the examples, the

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<sup>6</sup> “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” 66 FR 5447 at 5457 (January 19, 2001). ([Tissue Registration and Listing; Final Rule](#)).

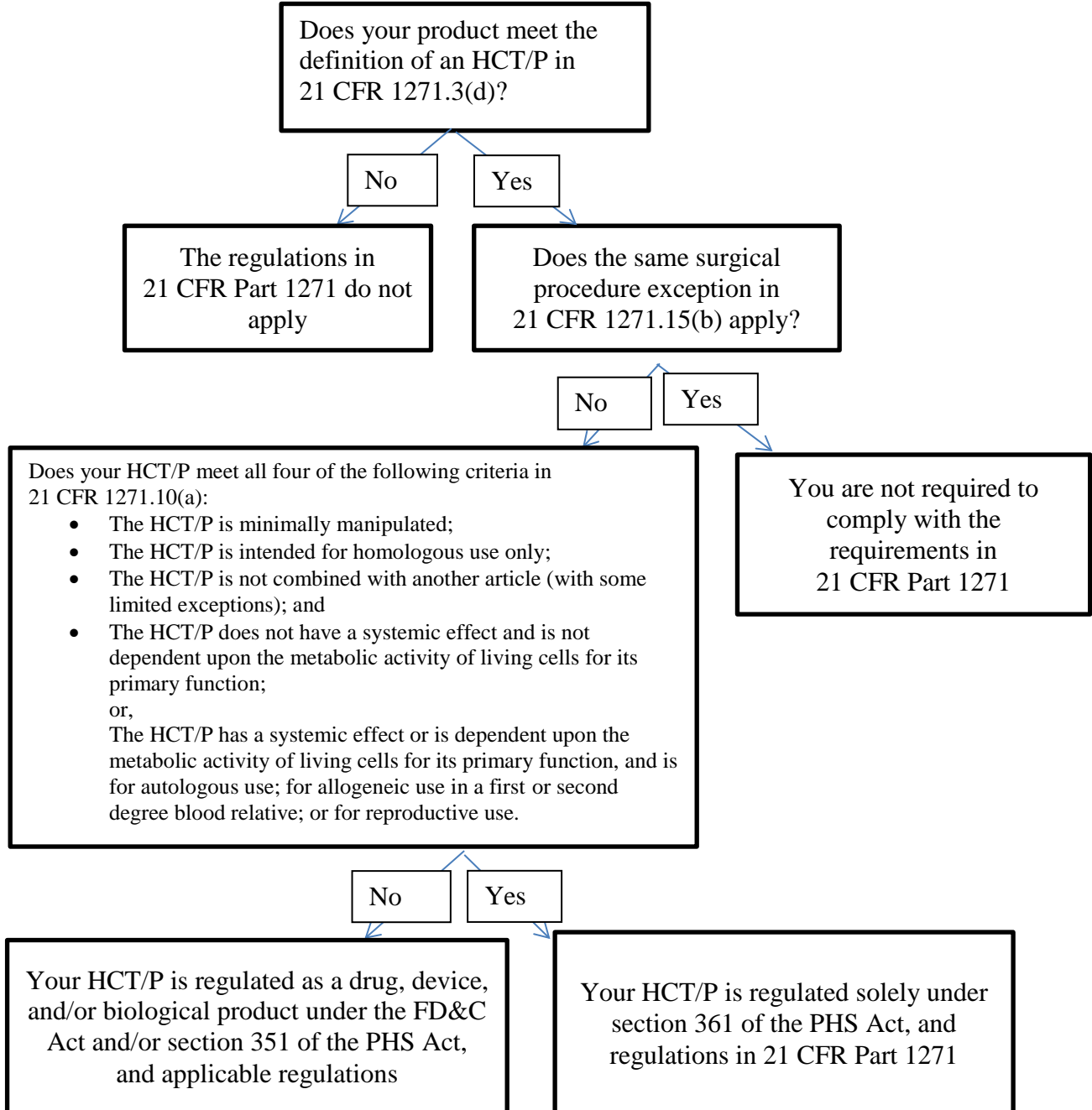
<sup>7</sup> See the proposed rule, “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products” 63 FR 26744 at 26748-26749 (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

<sup>8</sup> “Proposed Approach to Regulation of Cellular and Tissue-Based Products,” dated February 28, 1997 62 FR 9721 (March 4, 1997) page 19. ([1997 Proposed Approach](#)).

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HCT/Ps may fail to meet more than one of the four criteria in 21 CFR 1271.10(a). The following flowchart illustrates how manufacturers and healthcare providers should apply the criteria outlined in 21 CFR 1271.15(b)<sup>9</sup> and 1271.10(a) for HCT/Ps:

Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(b) and 1271.10(a)



<sup>9</sup> For additional information about applying the exception in 21 CFR 1271.15(b), see the “Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry” dated November 2017.



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### III. QUESTIONS AND ANSWERS REGARDING MINIMAL MANIPULATION

#### A. General Concepts

##### 1. How do the regulations define minimal manipulation?

Section 1271.3(f) provides two definitions of minimal manipulation, one that applies to structural tissue and one that applies to cells or nonstructural tissues. For structural tissue, minimal manipulation means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement (21 CFR 1271.3(f)(1)). For cells or nonstructural tissues, minimal manipulation means that the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3(f)(2)).

Original relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions. Similarly, relevant biological characteristics of cells or nonstructural tissues generally include the properties of the cells or nonstructural tissues in the donor that contribute to the cells or tissue's function(s). Processing that alters the original characteristics of the HCT/P, raises increased safety and effectiveness concerns for the HCT/P because there would be less basis on which to predict the product's function after transplantation.<sup>10</sup> Thus, the determination of whether an HCT/P is minimally manipulated is based on the effect of manufacturing on the original relevant characteristics of the HCT/P as the HCT/P exists in the donor, and not based on the intended use of the HCT/P in the recipient.

##### 2. Why is there a different definition of minimal manipulation for structural tissue and for cells or nonstructural tissue?

Under the regulations, HCT/Ps are considered either structural tissues or cells/nonstructural tissue, based on the characteristics of the tissue in the donor. This distinction, which was first described in the 1997 Proposed Approach for the regulation of cell and tissue-based products, is reflected in the definitions of minimal manipulation for structural tissue and cells/nonstructural tissue. Structural HCT/Ps generally raise different safety and efficacy concerns than do cells or nonstructural tissues.<sup>11</sup>

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<sup>10</sup> See the "Proposed Approach to Regulation of Cell and Tissue-Based Products" page 19. ([1997 Proposed Approach](#))

<sup>11</sup> See the "Proposed Approach to Regulation of Cell and Tissue-Based Products" page 20 (many structural HCT/Ps are conventional tissues with a long established history of safe use). ([1997 Proposed Approach](#))

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### **3. How do I determine whether an HCT/P is structural tissue or cellular/nonstructural tissue for purposes of applying the minimal manipulation criterion?**

To apply the minimal manipulation criterion, you first determine whether the HCT/P is structural or cellular/nonstructural. This determination is made based on the characteristics of the HCT/P in the donor, before recovery and before any processing that takes place. Then, you apply the appropriate definition to determine whether the HCT/P has been minimally manipulated.

HCT/Ps may perform multiple functions and FDA acknowledges that structural tissues contain cells. FDA also acknowledges that some manufacturers assert that an HCT/P has both a structural and cellular/nonstructural function. However, under the regulations, HCT/Ps are considered either structural tissues or cells/nonstructural tissues. HCT/Ps that physically support or serve as a barrier or conduit, or connect, cover, or cushion are generally considered structural tissues for the purpose of applying the HCT/P regulatory framework. Examples of structural tissue are provided in question 6 (see section III.B. of this document). HCT/Ps that serve metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions, are generally considered cells/nonstructural tissues for the purpose of applying the HCT/P regulatory framework. Examples of cells or nonstructural tissues are provided in question 15 (see section III.C. of this document).

### **4. What is processing of an HCT/P?**

Processing is defined as any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage (21 CFR 1271.3(ff)). Processing also includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization.

### **5. Which processing steps should be considered in determining whether an HCT/P is minimally manipulated?**

You should consider all of the processing steps.

## **B. Structural Tissue**

### **6. What types of tissues are considered structural tissues?**

Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues for the purposes of determining the applicable regulatory definition.

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Examples of structural tissues include:

- Bone;
- Skin;
- Amniotic membrane and umbilical cord;
- Blood vessel;
- Adipose tissue;
- Articular cartilage;
- Non-articular cartilage; and
- Tendon or ligament

### **7. Why is adipose tissue considered a structural tissue for the purpose of applying the HCT/P regulatory framework?**

Adipose tissue is typically defined as a connective tissue 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.<sup>12</sup> Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages.<sup>13</sup> Adipose tissue provides cushioning and support for other tissues, including the skin and internal organs, stores energy in the form of lipids, and insulates the body, among other functions. While adipose tissue has multiple functions, because it is predominantly composed of adipocytes and surrounding connective tissues that provide cushioning and support to the body, FDA considers adipose tissue to be a structural tissue for the purpose of applying the HCT/P regulatory framework.

To evaluate whether processing of adipose tissue would meet the regulatory definition of minimal manipulation, you should consider whether the processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support.

### **8. If my HCT/P is a structural tissue, how do I determine whether it is minimally manipulated?**

To evaluate whether processing of a structural tissue would meet the regulatory definition of minimal manipulation, you should consider whether the processing alters an original relevant characteristic of the tissue, relating to the tissue's utility for reconstruction, repair, or replacement as structural tissue.

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<sup>12</sup> 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>.

<sup>13</sup> Brown SA, Levi, B, Lequeux, C, et al. Basic Science Review on Adipose Tissue for Clinicians. *Plast. Reconstr. Surg.* 126:1936, 2010.

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### 9. What are original relevant characteristics of structural tissues?

Original relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions. For purposes of determining whether a structural HCT/P is minimally manipulated, a tissue characteristic is "original" if it is present in the tissue in the donor. A structural tissue characteristic is "relevant" if it could have a meaningful bearing on the tissue's utility for reconstruction, repair, or replacement. The structural tissue's utility for reconstruction, repair, or replacement relates to how that tissue functions in the donor. Examples of relevant characteristics of structural tissues include strength, flexibility, cushioning, covering, compressibility, and response to friction and shear.

### 10. How does changing the size or shape of the structural tissue affect whether an HCT/P is minimally manipulated?

Structural tissues may be processed by various machining and other mechanical methods to change the size or shape of the HCT/P. Such processing can be either minimal manipulation or more than minimal manipulation depending on whether the processing alters the original relevant characteristics of the structural tissue relating to its utility for reconstruction, repair, or replacement.

Example 10-1: Original relevant characteristics of bone relating to its utility to support the body and protect internal structures include strength, and resistance to compression. Milling, grinding, and other methods for shaping and sizing bone may generally be considered minimal manipulation when they do not alter bone's original relevant characteristics relating to its utility to support the body and protect internal structures.

- a. A manufacturer performs threading and other mechanical machining procedures to shape bone into dowels, screws, and pins. The HCT/Ps are generally considered minimally manipulated because the processing does not alter the bone's original relevant characteristics relating to its utility to support the body and protect internal structures.
- b. A manufacturer grinds bone to form bone chips and particles. The HCT/Ps would generally be considered minimally manipulated because the processing does not alter the bone's original relevant characteristics relating to its utility to support bodily structures.<sup>14</sup>

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<sup>14</sup> Refer to the "Jurisdictional Update: Human Demineralized Bone Matrix" dated January 19, 2001 (DBM Guidance) <https://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm106586.htm> for information relating to the regulatory classification of demineralized bone matrix (DBM). The guidance remains applicable to HCT/Ps that are DBM products. However, the DBM Guidance is based on factors that are specific to DBM products. The DBM Guidance document does not inform analyses to determine whether HCT/Ps other than DBM have been minimally manipulated and we do not consider it to be applicable to HCT/Ps other than DBM.

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- c. A manufacturer exposes bone to acid at elevated temperature to demineralize bone and dissolve collagen in order to form a gel. The HCT/P is generally considered more than minimally manipulated because the processing alters the bone's original relevant characteristics relating to its utility to support the body and protect internal structures.

Example 10-2: Original relevant characteristics of amniotic membrane relating to its utility to serve as a barrier generally include the tissue's physical integrity, tensile strength, and elasticity.

- a. A manufacturer processes amniotic membrane to preserve it and package it in sheets. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.
- b. A manufacturer grinds and lyophilizes amniotic membrane and packages it as particles. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.

Example 10-3: Original relevant characteristics of fascia lata, relating to its utility to cover muscle and aid in movement, generally include its strength, flexibility, and its fibrous, sheet-like configuration. A manufacturer grinds sheets of fascia lata into particles. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to cover muscle and aid in movement.

Example 10-4: The original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible connective tissue layer (dermis).

- a. A manufacturer processes skin by mechanical meshing and cryopreservation and packages it in sheets as meshed skin. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the skin relating to its utility as a protective covering.
- b. A manufacturer processes skin by removing the epidermis and then grinding the dermis into particles. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of skin related to its utility as a protective covering.

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### 11. How does removal of cells from structural tissue affect whether an HCT/P is minimally manipulated?

Structural tissues may contain both extracellular matrix and cellular components, and any alteration of these components that relates to the structural tissue's utility for reconstruction, repair, or replacement generally would be considered more than minimal manipulation. However, separation of structural tissue into components in which the original relevant characteristics relating to the tissue's utility for reconstruction, repair, or replacement are not altered generally would be considered minimal manipulation. For example, extraction or separation of cells from structural tissue in which the remaining structural tissue's original relevant characteristics relating to its utility for reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation.<sup>15</sup>

While some structural tissues may undergo processing that alters the cellular or extracellular matrix components without altering the original relevant characteristics of the tissue, the same processing may alter the original relevant characteristics of a different structural tissue. Therefore, to assess whether a processing step alters the original relevant characteristics of a structural tissue relating to its utility for reconstruction, repair, or replacement, you should consider the effects of the processing on the properties that contribute to the specific tissue's function in the donor, for each type of tissue you manufacture.

Example 11-1: Original relevant characteristics of adipose tissue relating to its utility to provide cushioning and support generally include its bulk and lipid storage capacity. A manufacturer processes adipose tissue by removing the cells, which leaves the decellularized extracellular matrix portion of the HCT/P. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to provide cushioning and support.

Example 11-2: Original relevant characteristics of the amniotic membrane related to its utility to serve as a barrier generally include its physical integrity, tensile strength, and elasticity. A manufacturer processes amniotic tissue to remove the chorion and other cells. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.

Example 11-3: The original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible connective tissue layer (dermis). A manufacturer processes skin to remove epidermis and freeze-dries and packages the remaining connective tissue, as

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<sup>15</sup> See the Proposed Rule "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26748. (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

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decellularized dermis. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a protective covering.

### **12. How does changing the physical state of the structural HCT/P affect whether it is minimally manipulated?**

In addition to mechanical methods, there are other types of processing that may alter the physical state of a structural tissue, such as chemical modification. If the mechanical, chemical, or other method of modification alters the HCT/P's physical state relating to its utility for reconstruction, repair, or replacement, then the HCT/P is generally considered more than minimally manipulated.

Example 12-1: The original relevant characteristics of cartilage relating to its utility to perform its load-bearing and other physical functions generally include firmness, smoothness, flexibility, and resistance to deformation. A manufacturer processes cartilage allograft by homogenizing it into a slurry. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to absorb shock and reduce friction between joints.

Example 12-2: The original relevant characteristics of ligament relating to its utility to attach bone to bone and aid in movement and stability generally include its tensile strength which is imparted by the bundled fibrous collagen. A manufacturer processes ligament to disaggregate the collagen fibers. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to aid in movement and stability.

### **13. How does storage affect whether a structural tissue is minimally manipulated?**

Storage that does not alter the original relevant characteristics of a structural tissue relating to its utility for reconstruction, repair, or replacement would generally be considered minimal manipulation. For example, an HCT/P that is placed in a tissue medium and refrigerated, such as stored in a buffer solution; or an HCT/P that is cryopreserved and stored in liquid nitrogen vapor, would generally meet the minimal manipulation criterion.<sup>16</sup>

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<sup>16</sup>According to 21 CFR 1271.10(a)(3), to meet the criteria for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271, 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.

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### **14. I isolate cells from structural tissue to produce a cellular therapy product. What definition of minimal manipulation would apply?**

If you isolate cells from structural tissue, the definition of minimal manipulation for structural tissue applies, regardless of the method used to isolate the cells. This is because the assessment of whether the HCT/P is a structural tissue or cellular/nonstructural tissue is based on the characteristics of the HCT/P as it exists in the donor, prior to recovery and any processing that takes place.

Example 14-1: Original relevant characteristics of adipose tissue relating to its utility to provide cushioning and support generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes (e.g., enzymatically digests, mechanically disrupts, etc.) the adipose tissue to isolate cellular components (with or without subsequent cell culture or expansion), commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The definition of minimal manipulation for structural tissue applies.

In this example, the HCT/P generally is considered more than minimally manipulated because the processing breaks down and eliminates the adipocytes and the surrounding structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement.

### **C. Cells or Nonstructural Tissues**

Under the regulatory framework for HCT/Ps, minimal manipulation of cells or nonstructural tissues is defined as processing that does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3(f)(2)).

### **15. What types of tissue are considered cells or nonstructural tissues?**

Cells or nonstructural tissues are generally those that serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions.

Examples of cells or nonstructural tissues include:

- Reproductive cells or tissues (e.g., oocytes);
- Hematopoietic stem/progenitor cells (e.g., cord blood)<sup>17</sup>;
- Lymph nodes and thymus;

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<sup>17</sup> Bone marrow is a source of hematopoietic stem/progenitor cells.

Minimally manipulated bone marrow for homologous use and not combined with another article (with certain exceptions), is not considered an HCT/P (21 CFR 1271.3(d)(4)). However, bone marrow that is more than minimally manipulated, intended by the manufacturer for a non-homologous use, or combined with another article with limited exceptions, meets the definition of an HCT/P and is subject to the regulations in 21 CFR Part 1271.



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- Parathyroid glands;
- Peripheral nerve; and
- Pancreatic tissue.

Secreted body fluids (e.g., amniotic fluid) are generally not considered HCT/Ps.<sup>18</sup> Cells from secreted body fluids are generally considered HCT/Ps, and the definition of minimal manipulation for cells or nonstructural tissues would apply.

### **16. What are relevant biological characteristics of cells or nonstructural tissues?**

Relevant biological characteristics of cells or nonstructural tissues generally include the properties of the cells or nonstructural tissues in the donor that contribute to the cells or tissue's function or functions.

Examples of relevant biological characteristics of cells or nonstructural tissues include differentiation and activation state, proliferation potential, and metabolic activity. Processing that alters any relevant biological characteristics of cells or nonstructural tissues generally would be considered more than minimal manipulation.

Example 16-1: Relevant biological characteristics of hematopoietic stem/progenitor cells generally include the ability to repopulate the bone marrow by self-renewal and by differentiating along myeloid and lymphoid cell lines.

- a. Hematopoietic stem/progenitor cells are circulating in increased numbers in the peripheral blood of a donor after administration of mobilizing agent. A manufacturer performs cell selection on the mobilized peripheral blood apheresis product to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation. The HCT/P would generally be considered minimally manipulated because the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristics to repopulate the bone marrow.
- b. A manufacturer uses hematopoietic stem/progenitor cells to produce terminally differentiated cells by culturing the cells under specific conditions. This HCT/P derived from hematopoietic stem/progenitor cells would generally be considered more than minimally manipulated because the processing alters the cells' relevant biological characteristics of multipotency and capacity for self-renewal.

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<sup>18</sup> 21 CFR 1271.3(d) states, "...The following articles are not considered HCT/Ps:...(3) secreted or extracted human products such as milk, collagen, and cell factors, except that semen is considered an HCT/P".

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- c. A manufacturer of a placental/umbilical cord blood product performs cell selection and incubates the selected cells in a laboratory vessel containing culture media and growth factors to achieve large numbers of cells capable of long-term repopulation of the bone marrow. This HCT/P derived from cord blood would generally be considered more than minimally manipulated because the processing affects the production of intracellular or cell-surface proteins and other markers of cell lineage, activation state, and proliferation, thereby altering the cells' relevant biological characteristics of multipotency and capacity for self-renewal.

### IV. QUESTIONS AND ANSWERS REGARDING HOMOLOGOUS USE

#### 17. What is the definition of homologous use?

Homologous use means 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 (21 CFR 1271.3(c)), including when such cells or tissues are for autologous use. We generally consider an HCT/P to be for homologous use when it is used to repair, reconstruct, replace, or supplement:

- Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,
- Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.<sup>19</sup>

Example 17-1: A heart valve is transplanted to replace a dysfunctional heart valve. This is homologous use because the donor heart valve performs the same basic function in the donor as in the recipient of ensuring unidirectional blood flow within the heart.

Example 17-2: Pericardium is intended to be used as a wound covering for dura mater defects. This is homologous use because the pericardium is intended to serve as a covering in the recipient, which is one of the basic functions it performs in the donor.

If an HCT/P is intended for use as an unproven treatment for a myriad of diseases or conditions, the HCT/P is likely not intended for homologous use only.<sup>20</sup>

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<sup>19</sup> "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26748-49 (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

<sup>20</sup> "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" 66 FR 5447 at 5457 (January 19, 2001). ([Tissue Registration and Listing; Final Rule](#))

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### **18. What does FDA mean by repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues?**

Repair generally means the physical or mechanical restoration of tissues, including by covering or protecting. For example, FDA generally would consider skin removed from a donor and then transplanted to a recipient in order to cover a burn wound to be a homologous use. Reconstruction generally means surgical reassembling or re-forming. For example, reconstruction generally would include the reestablishment of the physical integrity of a damaged aorta.<sup>21</sup> Replacement generally means substitution of a missing tissue or cell, for example, the replacement of a damaged or diseased cornea with a healthy cornea or the replacement of donor hematopoietic stem/progenitor cells in a recipient with a disorder affecting the hematopoietic system that is inherited, acquired, or the result of myeloablative treatment. Supplementation generally means to add to, or complete. For example, FDA generally would consider the implantation of dermal matrix into the facial wrinkles to supplement a recipient's tissues and the use of bone chips to supplement bony defects to be homologous uses. Repair, reconstruction, replacement, and supplementation are not mutually exclusive functions and an HCT/P could perform more than one of these functions for a given intended use.

### **19. What does FDA mean by “the same basic function or functions” in the definition of homologous use?**

For the purpose of applying the HCT/P regulatory framework, the same basic function or functions of HCT/Ps are considered to be those basic functions the HCT/P performs in the body of the donor, which, when transplanted, implanted, infused, or transferred, the HCT/P would be expected to perform in the recipient. It is not necessary for the HCT/P in the recipient to perform all of the basic functions it performed in the donor in order to meet the definition of homologous use. However, to meet the definition of homologous use, any of the basic functions that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor.

The basic function of an HCT/P is what it does from a biological/physiological point of view, or is capable of doing when in its native state.<sup>22</sup> By “basic” we mean the function or functions that are commonly attributed to the HCT/P as it exists in the donor. Basic functions are well understood; it should not be necessary to perform laboratory, pre-clinical, or clinical studies to demonstrate a basic function or functions for the purpose of applying the HCT/P regulatory framework. Also, clinical effects of the HCT/P in the

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<sup>21</sup> “Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement” 69 FR 68612 at 68643 (November 24, 2004) states, “HCT/Ps with claims for “reconstruction or repair” can be appropriately regulated solely under section 361 of the PHS Act, if such HCT/P meets all the criteria in § 1271.10, including minimal manipulation and homologous use.”

<sup>22</sup> “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products,” 63 FR 26744 at 26749 (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

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recipient that are not basic function or functions of the HCT/P in the donor would generally not be considered basic function or functions of the HCT/P for the purpose of applying the definition of homologous use.

Basic functions of a structural tissue would generally be to perform a structural function for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion.

Basic functions of a cellular or nonstructural tissue would generally be a metabolic or biochemical function, such as, hematopoietic, immune, and endocrine functions.

Example 19-1: Sources of hematopoietic stem/progenitor cells (HPCs) include cord blood, peripheral blood, and bone marrow.<sup>23</sup> The basic functions of HPCs include forming and replenishing the lymphohematopoietic system.

- a. HPCs from mobilized peripheral blood are intended for transplantation into an individual with a disorder affecting the hematopoietic system that is inherited, acquired, or the result of myeloablative treatment. This is homologous use because the peripheral blood product performs the same basic function of reconstituting the hematopoietic system in the recipient.
- b. HPCs from bone marrow are intended for infusion into an artery with a balloon catheter for the purpose of limiting ventricular remodeling following acute myocardial infarction. This is not homologous use because limiting ventricular remodeling is not a basic function of bone marrow.
- c. HPCs from cord blood are intended for intravenous infusion to treat cerebral palsy purportedly through the repair of damaged tissue in the brain through paracrine signaling or differentiation into neuronal cells. This is not homologous use because there is insufficient evidence to support that repair of neurologic tissue through paracrine signaling or differentiation into neuronal cells is a basic function of these cells in the donor.

Example 19-2: The basic functions of the cornea include protecting the eye and serving as its outermost lens. A corneal graft is transplanted to a patient with corneal blindness. This is homologous use because a corneal graft performs the same basic functions in the donor as in the recipient.

Example 19-3: The basic functions of a vein or artery include serving as a conduit for blood flow throughout the body. A cryopreserved vein or artery is used for arteriovenous access during hemodialysis. This is homologous use because the vein or artery is supplementing the vessel as a conduit for blood flow.

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<sup>23</sup> See “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue Based Products,” 63 FR 26744 at 26749 (May 14, 1998). ([Tissue Registration and Listing; Proposed Rule](#))

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Example 19-4: The basic functions of amniotic membrane include serving as a selective barrier for the movement of nutrients between the external and in utero environment, protecting the fetus from the surrounding maternal environment, and serving as a covering to enclose the fetus and retain fluid in utero.

- a. Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.
- b. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation<sup>24</sup> are not basic functions of amniotic membrane.
- c. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane.<sup>25</sup>

Example 19-5: The basic functions of pericardium include covering, protecting against infection, fixing the heart to the mediastinum, and providing lubrication to allow normal heart movement within chest. Autologous pericardium is used to replace a dysfunctional heart valve in the same patient. This is not homologous use because facilitating unidirectional blood flow is not a basic function of pericardium.

The use of an HCT/P from adipose tissue for the repair, reconstruction, replacement, or supplementation of adipose tissue would be considered a homologous use. 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. In contrast, the use of an HCT/P from adipose tissue for the treatment of a degenerative, inflammatory, or demyelinating disorder would generally be considered a non-homologous use.

Example 19-6: The basic functions of adipose tissue include providing cushioning and support for other tissues, including the skin and internal organs, storing energy in the form of lipids, and insulating the body.

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<sup>24</sup> Reducing scarring, angiogenesis, and inflammation are potential clinical effects in the recipient but are not basic functions of amniotic membrane in the donor; therefore, they are not considered homologous uses of amniotic membrane.

<sup>25</sup> Bio-Tissue 2001 RFD available at:

<https://www.fda.gov/downloads/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/RedactedDecisionLetters/UCM113701.pdf>.

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- a. Adipose tissue is used to fill voids in the face or hands (e.g., for cosmetic reasons). This is homologous use because providing cushioning and support, is a basic function of adipose tissue.<sup>26</sup>
- b. An HCT/P from adipose tissue is used to treat musculoskeletal conditions such as arthritis or tendonitis by regenerating or promoting the regeneration of articular cartilage or tendon. This is generally not considered a homologous use because regenerating or promoting the regeneration of cartilage or tendon is not a basic function of adipose tissue.
- c. An HCT/P from adipose tissue is used to treat neurological disorders such as multiple sclerosis by limiting the autoimmune reaction and promoting remyelination. This is generally not considered a homologous use because limiting the autoimmune reaction and promoting remyelination are not basic functions of adipose tissue.
- d. Adipose tissue is used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is homologous use because providing cushioning and support is a basic function of adipose tissue.<sup>27</sup>

### **20. Does my HCT/P have to be used in the same anatomic location to perform the same basic function or functions?**

An HCT/P may perform the same basic function or functions even when it is not used in the same anatomic location where it existed in the donor.<sup>28</sup> A transplanted HCT/P could replace missing tissue, or repair, reconstruct, or supplement tissue that is missing or damaged, either when placed in the same or different anatomic location, as long as it performs the same basic function(s) in the recipient as in the donor.

Example 20-1: The basic functions of skin include covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment. The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.

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<sup>26</sup> Some cosmetic procedures involving reimplantation of autologous adipose tissue that is only rinsed or cleansed may meet the exception in 21 CFR 1271.15(b). For additional information about applying the exception in 21 CFR 1271.15(b), see the “Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry” dated November 2017.

<sup>27</sup> Some breast reconstruction or augmentation procedures involving re-implantation of autologous adipose tissue that is only rinsed or cleansed may meet the exception in 21 CFR 1271.15(b). For additional information about applying the exception in 21 CFR 1271.15(b), see the “Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry” dated November 2017.

<sup>28</sup> “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” 66 FR 5447 at 5457 (January 19, 2001). ([Tissue Registration and Listing; Final Rule](#))

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- a. An acellular dermal product is used for supplemental support, protection, reinforcement, or covering for a tendon. This is homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.
- b. An acellular dermal product is used for tendon replacement or repair. This is not homologous use because serving as a connection between muscle and bone is not a basic function of dermis.

Example 20-2: The basic functions of bone are supporting the body and protecting internal structures such as the brain. Allogeneic mineralized or demineralized cortical human bone is used to supplement the recipient's bone for repair, replacement, and reconstruction of bony voids or gaps involving the extremities, cranium, and spinal column; or for augmentation for posterior lateral fusions in the spinal column. These are homologous uses because in all locations, the HCT/P is supplementing the recipient's bone, for the purpose of supporting the body or protecting internal structures.

Example 20-3: The basic functions of pancreatic islets include regulating glucose homeostasis within the body. Pancreatic islets are transplanted into the liver through the portal vein for preservation of endocrine function after pancreatectomy. This is homologous use because the regulation of glucose homeostasis is a basic function of pancreatic islets.

### **21. What does FDA mean by “intended for homologous use” in 21 CFR 1271.10(a)(2)?**

The regulatory criterion in 21 CFR 1271.10(a)(2) states that the HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent.

Labeling includes the HCT/P label and any written, printed, or graphic materials that supplement, explain, or are textually related to the product, and which are disseminated by or on behalf of its manufacturer.<sup>29</sup> Advertising includes information, other than labeling, that originates from the same source as the product and that is intended to supplement, explain, or be textually related to the product (e.g., print advertising, broadcast advertising, electronic advertising (including the Internet), statements of company representatives).<sup>30</sup>

An HCT/P is intended for homologous use when its labeling, advertising, or other indications of the manufacturer's objective intent refer to only homologous uses for the HCT/P. When an HCT/P's labeling, advertising, or other indications of the manufacturer's objective intent refer to non-homologous uses, the HCT/P would not meet the homologous use criterion in 21 CFR 1271.10(a)(2).

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<sup>29</sup> “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” 66 FR 5447 at 5457 (January 19, 2001). ([Tissue Registration and Listing; Final Rule](#))

<sup>30</sup> *Id.*

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### **22. What does FDA mean by “manufacturer’s objective intent” in 21 CFR 1271.10(a)(2)?**

A manufacturer’s objective intent is determined by the expressions of the manufacturer or its representatives, or may be shown by the circumstances surrounding the distribution of the article. A manufacturer’s objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by the manufacturer or its representatives. It may be shown by surrounding circumstances under which a HCT/P is offered for a purpose for which it is neither labeled nor advertised.

## **V. REGULATORY SCOPE AND COMPLIANCE POLICY**

### **A. Scope of FDA’s Regulation of HCT/Ps**

As noted in the Background section of this document, this guidance only applies to products and establishments that are subject to FDA’s regulations in 21 CFR Part 1271. Establishments that meet the same surgical procedure exception in 21 CFR 1271.15(b) are not subject to FDA’s regulations in 21 CFR Part 1271. This guidance also does not apply to products that fall outside the definition of HCT/P in 21 CFR 1271.3(d). For example, platelet rich plasma (PRP, blood taken from an individual and given back to the same individual as platelet rich plasma) is not an HCT/P under Part 1271 because it is a blood product. Accordingly, FDA does not apply the criteria in 21 CFR 1271.10(a) to PRP, and PRP is outside the scope of this guidance.

### **B. Compliance and Enforcement Policy Regarding Certain Regulatory Requirements**

To give manufacturers time to determine if they need to submit an IND or marketing application in light of this guidance and, if such an application is needed, to prepare the IND or marketing application, for the first 36 months following issuance of this guidance FDA generally intends to exercise enforcement discretion with respect to the IND and the premarket approval requirements for HCT/Ps that do not meet one or more of the 21 CFR 1271.10(a) criteria, provided that the HCT/P is intended for autologous use and its use does not raise reported safety concerns or potential significant safety concerns.

FDA intends to focus enforcement actions on products with higher risk, taking into account factors such as whether the product is for non-autologous (allogeneic) use and the route and site of administration. For example, actions related to products with routes of administration associated with a higher risk (e.g., those administered by intravenous injection or infusion, aerosol inhalation, intraocular injection, or injection or infusion into the central nervous system) will be prioritized over those associated with a lower risk (e.g., those administered by intradermal, subcutaneous, or intra-articular injection). HCT/Ps that are intended for non-homologous use, particularly those intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions, are also more likely to raise significant safety concerns than HCT/Ps intended for



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homologous use because there is less basis on which to predict the product's behavior in the recipient, and use of these unapproved products may cause users to delay or discontinue medical treatments that have been found safe and effective through the New Drug Application or BLA approval processes.

Regenerative medicine is a complex and rapidly evolving field. Accordingly, FDA will continue to reassess its application of the HCT/P regulatory framework, including the minimal manipulation and homologous use criteria in 21 CFR 1271.10(a), as additional scientific evidence emerges in this field.

## VI. ADDITIONAL INFORMATION

### **23. What regulations apply if my HCT/P is regulated as a biological product?<sup>31</sup>**

HCT/Ps that are regulated as biological products are subject to section 351 of the PHS Act and the FD&C Act and require premarket approval. Such HCT/Ps are subject to the applicable drug regulations, including the requirements in 21 CFR Parts 210 and 211, and the applicable requirements in 21 CFR 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. Pursuant to these regulations, you are required to register as an establishment, and list your HCT/Ps (21 CFR 1271.1(b)(2)) (see section VI. question 25 of this document).

In order to lawfully market a biological product, a biologics license must be in effect (PHS Act) (42 U.S.C. 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 IND application in effect in accordance with the FD&C Act (21 U.S.C. 355(i)) and FDA regulations (21 CFR Part 312 and 21 CFR 601.21). See section VI. question 27 of this document about obtaining more information regarding the IND process.

### **24. What must I do if my HCT/P 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 VI. question 25 of this document);
- 2) Submit to FDA a list of each HCT/P manufactured; and

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<sup>31</sup> Some HCT/Ps may be regulated as devices. For more information about device regulation, see CDRH's webpage Device Advice – Overview of Medical Device Regulation at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm>.

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- 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)).

### **25. Must 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 of products with the Agency. If you are a manufacturer that is required to register, you must do so within five days after beginning operations (21 CFR 1271.21(a)). Registrations must be updated annually in December (21 CFR 1271.21(b)), except if the ownership or location of the establishment changes, or if there is a change in the United States agent's name, address, telephone number, or email address, in which case, you must submit an amendment to the registration within 30 calendar days of the change (21 CFR 1271.26).

### **26. How can I get more information about the appropriate regulatory considerations for my HCT/P?**

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 that includes 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: <https://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: <https://www.fda.gov/CombinationProducts/RFDProcess/default.htm>. Additional information may be found at <https://www.fda.gov/Regulatoryinformation/Guidances/ucm126053.htm>. You

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may also submit a Pre-RFD to OCP to obtain preliminary feedback on the classification for your HCT/P as well as assistance on how to prepare an RFD. Additional information may be found at

<https://www.fda.gov/Regulatoryinformation/Guidances/ucm126053.htm>.

**27. How can I obtain more information about the IND process for my HCT/P that requires premarket approval?**

Further information about IND requirements for biological products may be obtained through the Division of Regulatory Project Management, Office of Tissues and Advanced Therapies, at 240-402-8190 or <mailto:OTATRPMS@fda.hhs.gov>.