

Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

Draft Guidance for Industry and Food and Drug Administration Staff

This guidance document is for comment purposes only.

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For questions on the content of this guidance, contact CBER, Office of Communication, Outreach, and Development (OCOD) at 240-402-7800 or 800-835-4709. For questions about this document concerning products regulated by CDRH, contact the Office of the Center Director at 301-796-5900. If you need additional assistance with regulation of combination products, contact the Office of Combination Products at 301-796-8930.

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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Draft Guidance for Industry and Food and Drug Administration Staff

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic.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 FDA staff responsible for implementing this guidance using the contact information on the title page of this guidance.

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 recommendations for meeting the criterion under Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically the 21 CFR 1271.10(a)(1) criterion of minimal manipulation. The interpretation of the minimal manipulation criterion and definitions of related key terms has been of considerable interest to industry stakeholders since the criterion and definitions were first proposed during the Agency's rulemaking on HCT/Ps. It is anticipated that this guidance will improve stakeholders' understanding of the definitions of minimal manipulation in 21 CFR 1271.3(f), and how to apply the regulatory criterion in 21 CFR 1271.10(a)(1) to their HCT/Ps.¹ This guidance, when finalized, will supersede the guidance entitled "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update" dated September 2006 (2006 Guidance). When finalized, this guidance will reflect the Agency's current thinking on this topic.

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.

¹ 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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II. BACKGROUND

HCT/Ps are defined in § 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.² FDA has implemented a risk-based approach to the regulation of HCT/Ps. Under the authority of section 361 of the PHS Act, FDA established regulations for all HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases. These regulations can be found in 21 CFR Part 1271.

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 § 1271.10(a), and the establishment that manufactures the HCT/P does not qualify for any of the exceptions in 21 CFR 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under the Federal Food,

² 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))

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Drug and Cosmetic Act (FD&C Act), and/or section 351 of the PHS Act, and applicable regulations, including 21 CFR Part 1271, and pre-market review will be required.

Section 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 21 CFR Part 1271 is that the HCT/P is minimally manipulated. As defined in 21 CFR 1271.3(f), minimal manipulation means:

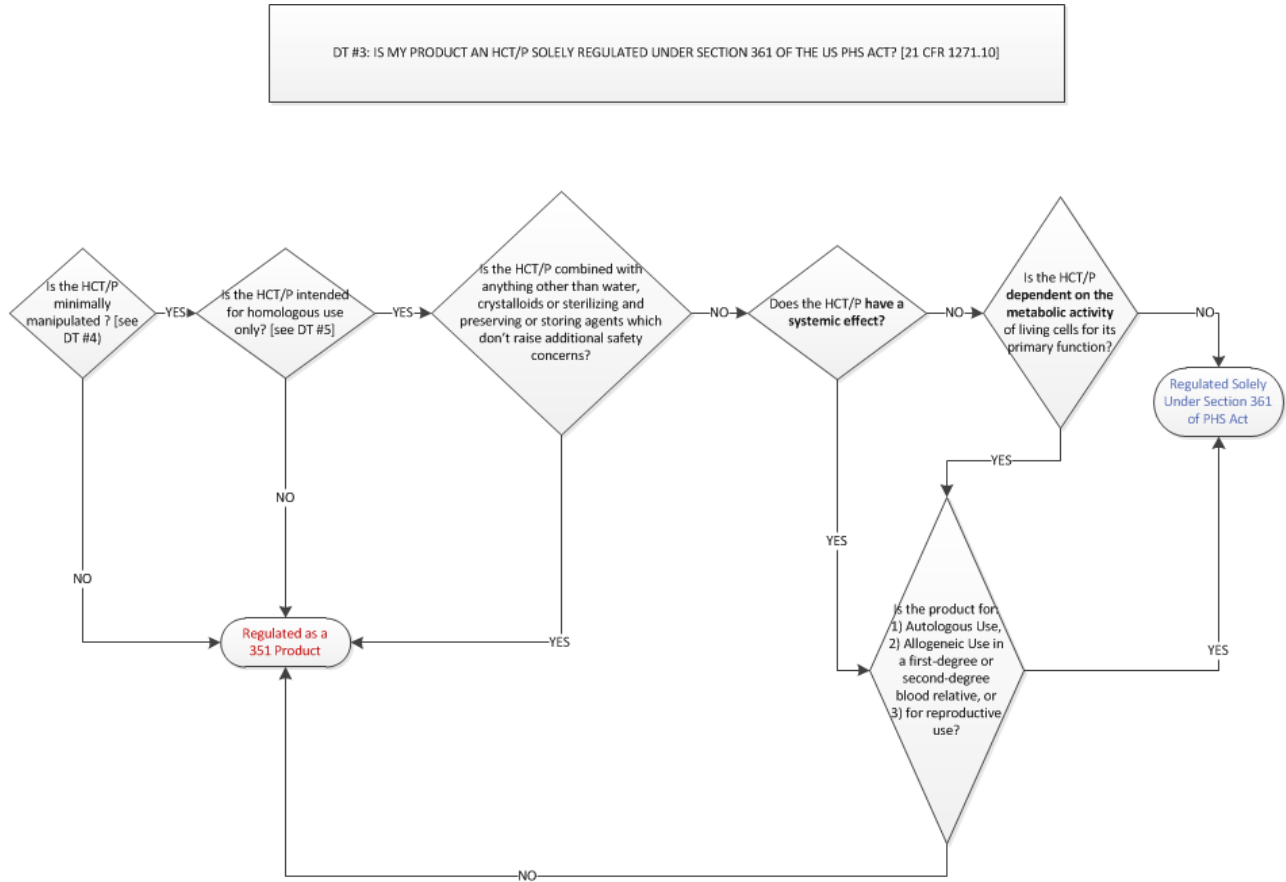
- 1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
- 2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of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

Since the discussion of these terms in the preamble to the HCT/P Establishment Registration and Listing final rule,³ FDA has published 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 § 1271.10(a)(1). When finalized, this guidance will supersede the 2006 Guidance.

This guidance includes examples of HCT/Ps that are and are not minimally manipulated, based on inquiries we have received, and provides general principles that can be applied to HCT/Ps that may be developed in the future. 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 1271.⁴

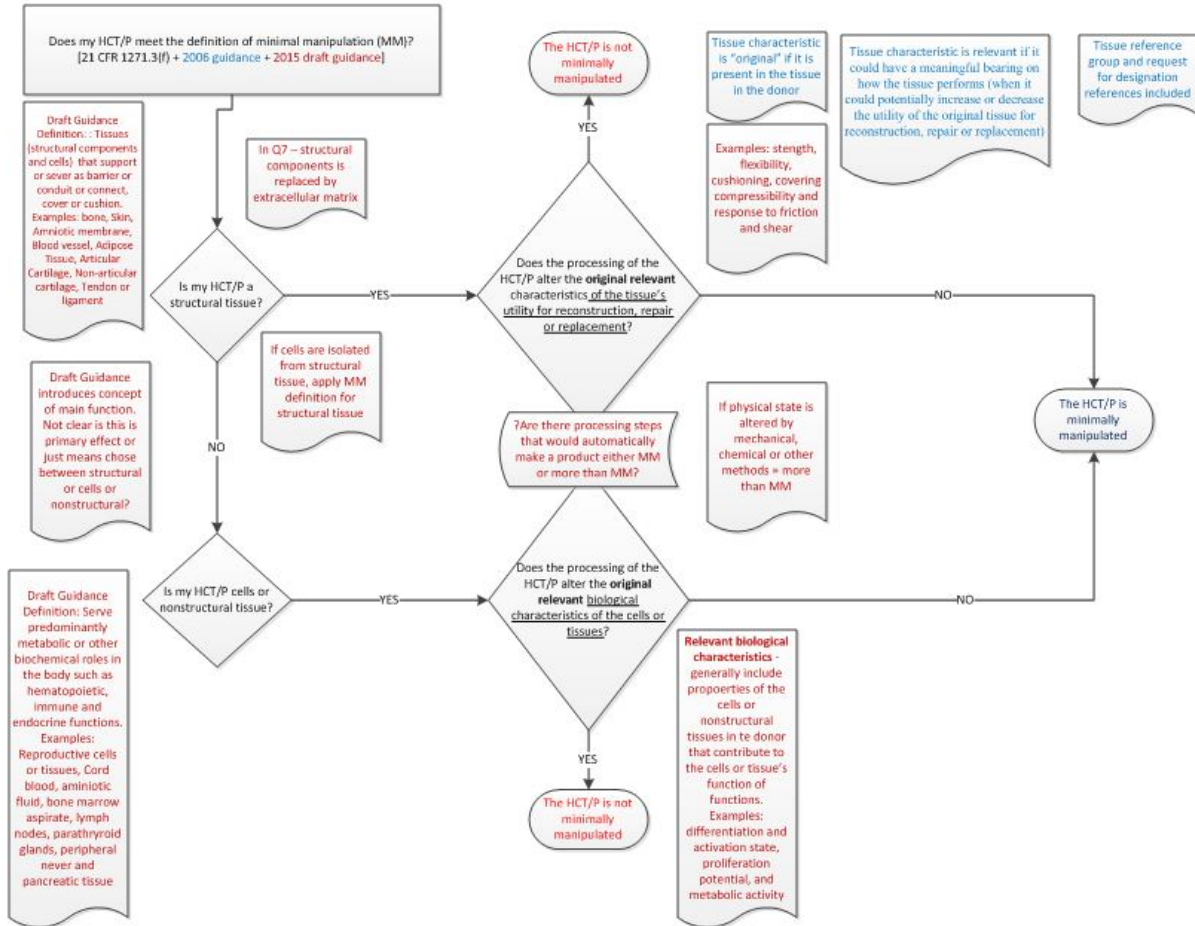
ARM COMMENT: The Alliance for Regenerative Medicine (ARM) believes this Guidance Document would be significantly enhanced by the addition of flow charts to clearly demonstrate the Agency's thinking in how to evaluate these products. This has been done in other areas and is very useful for the Agency and Industry. Following is an example flow chart that would be very useful for Industry.

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ARM COMMENT: The following chart contains the information from the regulations and guidance documents and it would be very helpful for industry if the Agency converted the regulations and guidance into a useful flowchart published in this guidance. Specifically it would be most helpful for industry if there was an order of assessment of Agency criteria in a logical sequence. The criteria provided in the figure below do not represent ARM thinking and are solely provided to represent the current industry view of Agency information.

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ARM COMMENT:

The Alliance for Regenerative Medicine feels that this Guidance document is generally silent to the decision Tissue Reference Group (TRG) and believe this Guidance would benefit from the following:

An Appendix should be added to this guidance document that reflects TRG decision making and the process by which TRG makes decisions. This is another location where flowcharts would be very helpful to industry. We also believe the TRG website should be maintained current within one quarter of activity.

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III. QUESTIONS AND ANSWERS

A. General Concepts

1. How do the regulations define minimal manipulation?

Section 1271.3(f) provides two definitions of minimal manipulation. 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)).

³ "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" 66 FR 5447 at 5457 (January 19, 2001).

⁴ See the proposed rule, "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26748-49 (May 14, 1998).

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

The main function of the HCT/P, in the donor, determines which definition of minimal manipulation applies.⁵ For example, tissues 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 regulatory framework. Structural tissue is composed of structural components and cells, and those cells are part of the structural tissue for the purposes of determining which definition of minimal manipulation applies. Examples of structural tissue are provided in question 5 (see section III.B. of this document).

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 are provided in question 11 (see section III.C. of this document).

ARM COMMENT: The Alliance of Regenerative Medicine is concerned regarding the use of a ‘new’ term ‘main function’ which is not currently a term used in the regulations. If FDA is going to use the term ‘main function’ to further define the regulations it needs to be properly defined and not in a ‘such as’ manner as there are products on the market and currently under development.

3. 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 generally includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization.

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

You should consider all of the processing steps.

ARM COMMENT: The Alliance for Regenerative Medicine would like the Agency to confirm that the previously released 2001 list of processing steps in the Preamble to the 21 CFR Part 1271 regulation (Federal Register: January 19, 2001 (Vol 66, N 13) : “At this time, examples of HCT/P’s that we consider to be minimally manipulated include those that have been subjected to the following

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procedures: Density gradient separation; selective remove of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing.”) that the Agency had determined to be minimally manipulated remains current Agency thinking. If the Agency thinking has evolved since 2001, we request that the draft guidance identify under what circumstances, if any, the criteria outlined in 2001 would not constitute minimal manipulation. Centrifugation should be specifically be called out as a minimal manipulation except where it may affect relevant characteristics of the tissue being centrifuged. This would bring the FDA’s guidance in line with the European Advanced Therapy Medicinal Products (ATMPs) guidance which is followed more or less by most OUS regulatory authorities. The use of appropriate anticoagulants in the context of centrifugation should also be called out as minimal manipulation unless the addition of such substances may affect relevant characteristics of the tissue being centrifuged.

B. Structural Tissue

5. 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.

⁵ See the Proposed Rule at 26749.

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Examples of structural tissues include:

- Bone: supports the body and protects internal structures, such as the brain;
- Skin: provides a barrier to retain moisture and protect from infection and/or the external environment;
- Amniotic membrane: serves as a covering;
- Blood vessel: acts as a conduit;
- Adipose tissue: provides padding and cushioning against shocks and stores fat;
- Articular cartilage: reduces friction and serves as a shock absorber;
- Non-articular cartilage: provides structural support and serves as a shock absorber; and
- Tendon or ligament: connects components of the skeletal system and aids in mobility.

6. 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.

ARM COMMENT: The Alliance for Regenerative Medicine believes the guidance should clarify (with more examples) at what level a tissue's structure must be preserved in order to be considered to be minimally manipulated. The guidance implies, but does not explicitly state, that the primary structure, including the load bearing properties of the tissue, may be changed so long as the underlying tissue structure is unaffected. A process is considered to be minimally manipulated unless the process "alters an original relevant characteristic of the tissue, relating to the tissues' utility for reconstruction, repair, or replacement as structural tissue." This raises the question, does a structural tissue in every case have to fulfill a structural function at the time it is implanted? For example, grinding and demineralization of bone are considered minimal manipulation even though these processes affect the load bearing properties of the tissue. This is true because the underlying structure of the bone tissue is preserved, and the utility of the bone tissue for bone repair (i.e. bone grafting), is not compromised by these processes. When considering enforcement actions related to amnion when compared to bone, Agency thinking appears to be inconsistent.

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Please add relevant examples drawn from recent TRG decisions, including:

- **Allogeneic bone product composed of frozen cortical bone, Milled into micro-sized granules, the Allogeneic bone product composed of frozen cortical bone, Milled into micro-sized granules is minimally manipulated due to the fact the relevant characteristics of the tissue related to its utility for repair are unaltered.**
- **Allograft bone product in mineralized or demineralized form, soaked in antibiotic during processing to reduce bioburden of the allograft, minimally manipulated due to the fact the relevant characteristics of the tissue related to its utility for repair are unaltered.**

Please add well established examples of minimal manipulation such as:

- **Centrifugation of bone tissue to separate out the marrow and hematopoietic elements. The underlying structure and properties of the bone tissue remain and its utility for bone repair and/replacement is unaltered by the centrifugation process.**

7. What are original relevant characteristics of structural tissues?

ARM COMMENT: The Alliance for Regenerative Medicine believes FDA does not provide adequate definition of ‘relevant’ such that the area continues to appear to be discretionary when considering enforcement actions.

Original relevant characteristics of structural tissues generally include the properties of that tissue in the donor. 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. Examples of relevant characteristics of structural tissues include strength, flexibility, cushioning, covering, compressibility, and response to friction and shear.

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 relevant characteristics relating to 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 relevant characteristics relating to reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation.⁶

⁶ See the Proposed Rule at 26748.

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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 tissue type. Therefore, to assess whether a processing step alters the original relevant characteristics of a structural tissue, 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 7-1: Original relevant characteristics of amniotic membrane to serve as a membranous barrier generally include the tissue's physical integrity, tensile strength, and elasticity.

- a. A manufacturer mechanically and chemically processes amniotic membrane to remove cells and packages it in sheets as decellularized amniotic membrane. The HCT/P generally is considered minimally manipulated because the removal of the cellular component does not alter the utility of the HCT/P to serve as a membranous barrier.
- b. A manufacturer grinds and lyophilizes amniotic membrane and packages it as a powder. The HCT/P generally is considered more than minimally manipulated because the processing alters the membrane's physical integrity, tensile strength, and elasticity that allow it to serve as a membranous barrier.

Example 7-2: Original relevant characteristics of skin to serve as a water-resistant barrier to pathogens and other damaging agents in the external environment generally include its large surface area and dense connective tissue layer. A manufacturer mechanically and chemically processes skin to remove epidermis and some connective tissue components, freeze-dries the remaining connective tissue components, and packages it in sheets as a decellularized allogeneic dermal graft. The HCT/P generally is considered minimally manipulated because the removal of the cellular components does not alter the utility of the HCT/P to serve as a barrier.

Example 7-3: Original relevant characteristics of adipose tissue to pad and cushion against shocks 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 HCT/P's ability to provide padding and cushioning.

Example 7-4: Original relevant characteristics of ligament generally include tensile strength, imparted by the fibrous collagen content, and ability to attach bone to bone and aid in movement and stability. A manufacturer processes ligament by chemically altering the degree of crosslinking of the collagen. The HCT/P generally is considered more than minimally manipulated because the crosslinking impedes the

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normal cellular remodeling and integration of the HCT/P, thereby altering the ligament's tensile strength, relating to its utility for reconstruction, repair, or replacement of a ligament.

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

Processing of HCT/Ps may change the size or shape of the structural tissue through various means, such as machining and other mechanical methods. Determining whether such processing alters the original relevant characteristics of the structural tissue is based on whether the changes relate to the HCT/P's utility for reconstruction, repair, or replacement.

Grinding and fragmentation are examples of processing that can be either minimal or more than minimal manipulation depending on whether the processing alters the original relevant characteristics of the structural tissue related to its utility for reconstruction, repair, or replacement.

Example 8-1: Grinding and shaping bone does not alter its inherent physical properties such as compressibility and strength. Threading and other mechanical machining procedures that are performed to create bone dowels, screws, and pins also are generally considered minimal manipulation because the processing does not alter the bone's inherent physical properties. Additionally, bone dowels, and bone chips for repair, reconstruction, or replacement of periodontal bone are examples of types of HCT/Ps that are generally considered minimally manipulated because the bone's inherent physical properties are not altered.⁷

9. How does changing the physical state of the structural tissue 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 9-1: The original relevant characteristics of cartilage to perform its load-bearing and other physical functions generally include firmness, smoothness, and flexibility. A cartilage allograft that is homogenized (changed from a solid to a slurry

⁷ Refer to the "Jurisdictional Update: Human Demineralized Bone Matrix" (January 19, 2001) (DBM Guidance) 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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or gel) generally is considered more than minimally manipulated because the processing alters the utility of the HCT/P to absorb shock and reduce friction between joints.

10. 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, you should apply the definition of minimal manipulation for structural tissue.

Example 10-1: Original relevant characteristics of adipose tissue, a structural tissue, to pad and cushion against shocks generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes the adipose tissue to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The HCT/P generally is considered more than minimally manipulated because the processing breaks down and eliminates the 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.

ARM COMMENT: The Alliance of Regenerative Medicine it would be helpful to have a positive example of where adipose tissue would be considered to be minimally manipulated.

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)).

11. 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);
- Cord blood;
- Amniotic fluid;
- Bone marrow aspirate;
- Lymph nodes;
- Parathyroid glands;

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- Peripheral nerve; and
- Pancreatic tissue.

12. 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 relevant biological characteristics of cells or nonstructural tissues generally would be considered more than minimal manipulation.

Example 12-1: 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. A manufacturer performs cell selection on a 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 cell-selected peripheral blood stem cells are not altered with regard to their relevant biological characteristics relating to repopulating the bone marrow.
- b. 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.