ALLIANCE for Regenerative Medicine

August 24, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm 1061
Rockville, MD, 20852

To Whom It May Concern:

The Alliance for Regenerative Medicine is pleased to provide the Food and Drug Administration (FDA) with the attached comments to the FDA Draft Guidance for Industry and FDA Staff on Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products dated October 2015. Instead of providing comments in a stand-alone document, ARM has inserted its comments directly in the Draft Guidance. In addition, a few general comments are provided below.

ARM welcomes this new guidance and believes it will be very useful for Sponsors developing human cells, tissues and cellular and tissue-based products (HCT/Ps).

General Comments:

- This Guidance contains a lot of precise terminology. Adding a Glossary with the definition of the key terms used in the Guidance may be helpful to provide further clarity on how these terms should be interpreted and understood in the context of the development of HCT/Ps. Alternatively, adding a reference in the Guidance to the definitions provided in 1271.3, and ensuring that these definitions reflect the Agency's current thinking may be sufficient.

- Throughout the Guidance, it would be useful for FDA to provide more detailed examples - positive examples where HCT/Ps met the criteria for homologous use; as well as negative examples where HCT/Ps did not meet the criteria for homologous use.

We look forward to the opportunity to share a summary of our comments during the Public Hearing scheduled on September 12th and 13th, and to the publication of the final Guidance. We thank the FDA in advance for taking into account the comments received on this Guidance from all parties, including the Alliance for Regenerative Medicine.

Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

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Draft Guidance for Industry and FDA Staff

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of this guidance, contact CBER, Office of Communications, Outreach and Development (OCOD) at 800-835-4709 or 240-402-8010. For questions about this document concerning products regulated by CDRH, contact the Office of the Center Director at 301-796-5900. If you need assistance with regulation of combination products, contact the OCP at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)
October 2015

Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products Draft

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Guidance for Industry and FDA Staff *Additional*

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Draft Guidance for Industry and FDA Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are providing you, human cells, tissues, and cellular and tissue-based product (HCT/P) establishments, health care providers, and FDA staff, with recommendations for applying Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically the 21 CFR 1271.10(a)(2) criterion of homologous use. The interpretation and application of the homologous use criterion and related definitions have been of considerable interest to industry stakeholders since being proposed during the Agency's rulemaking on HCT/Ps. This guidance, when finalized, will improve stakeholders' understanding of the definition of homologous use in 21 CFR 1271.3(c), and how to apply the regulatory criterion in 21 CFR 1271.10(a)(2) to their HCT/Ps.

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

II. BACKGROUND

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.[1] 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 all of the criteria 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, the HCT/P will be regulated as a drug, device, and/or biological product under the Federal Food, 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.

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[1] 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))

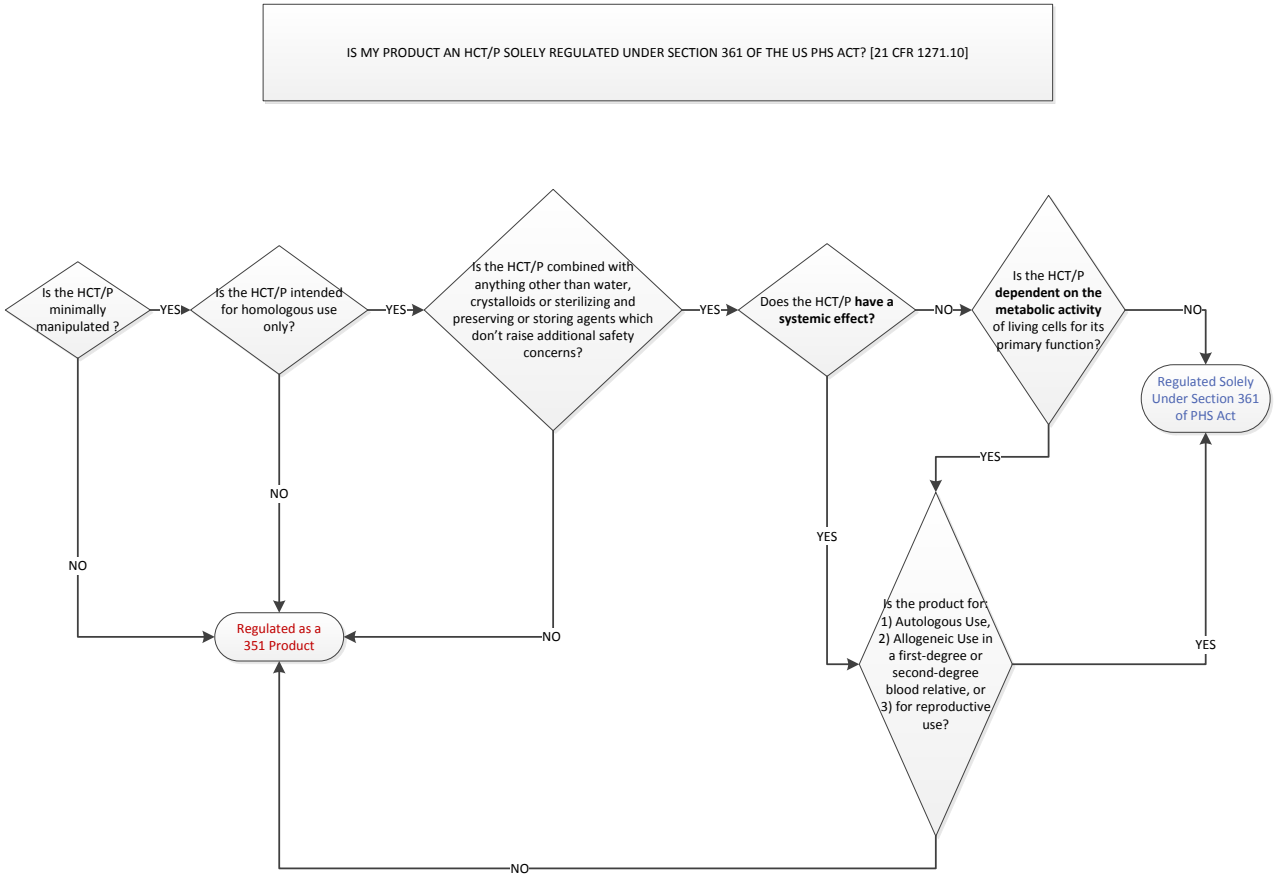
Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act is that the "HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." 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).[2] In applying the homologous use criterion, FDA will determine what the intended use of the HCT/P is, as reflected by the ~~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 homologous use criterion in 21 CFR 1271.10(a)(2). 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 regulation in 21 CFR 1271.10(a)(2) applies 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 HCT/Ps may fail to meet more than one of the four criteria in 21 CFR 1271.10(a).

ARM Comment #1:

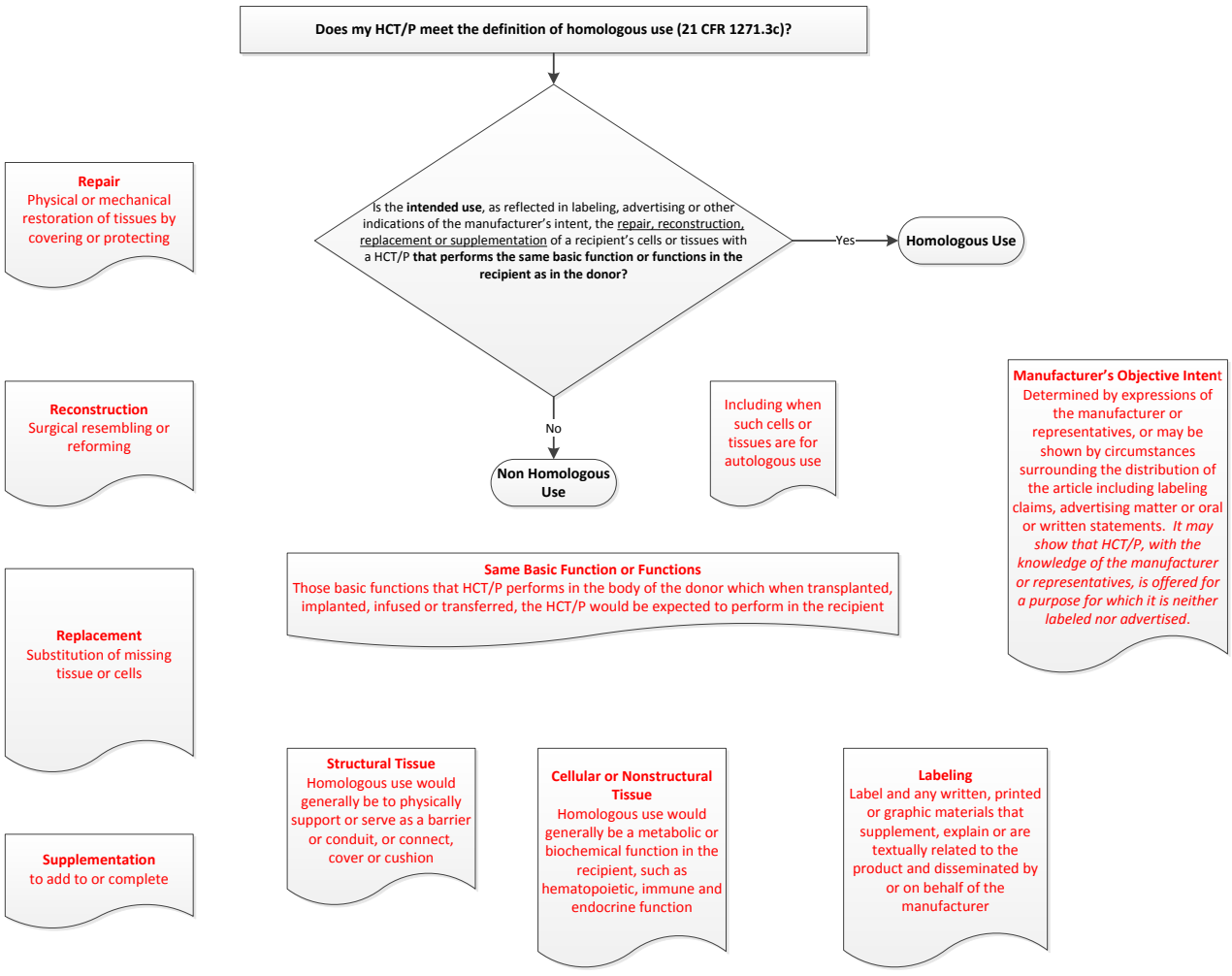
The Alliance for Regenerative Medicine (ARM) believes this Guidance would be significantly enhanced by the addition of flow charts to clearly demonstrate the Agency's thinking in how to evaluate HCT/Ps. This has been done in other areas and is very useful for the industry. Flow charts have the potential to provide additional transparency on the steps and criteria used by the Agency to make decisions. Below is an example of such a flow chart that would be very useful to include in this Section of the Guidance. ARM would welcome further collaboration with FDA on creating additional flow charts if helpful.

Proposed Flow Chart – Is my product an HCT/P solely regulated under Section 361 of the US PHS Act (21 CFR 1271.10)?



ARM Comment #2: In addition, ARM believes it would be useful to include in this Guidance another flow chart to help Sponsors determine whether or not their HCT/P meets the definition of homologous. Specifically, it would be most helpful if there was an order of assessment of the Agency's criteria in a logical sequence. The general flow chart provided below including the criteria described in it are not meant to represent ARM's thinking. Rather the general flow chart is provided to the Agency to illustrate what the Agency's final flowchart could look like, and to represent the broad amount of relatively complex information industry has to interpret to make a determination on homologous use. The specific criteria issued by the Agency in this Guidance should be consistent with current regulations and FDA's interpretations description.

General illustrative flow chart to help decide whether an HCT/P meets the definition of homologous use



ARM Comment #3: The Alliance for Regenerative Medicine finds that this Guidance document is generally silent to the recommendations made by the FDA Tissue Reference Group (TRG) and believe this Guidance would benefit from an Appendix describing the process used by TRG to make recommendations. It would also be useful to include in this Guidance a reference to where the TRG recommendations are published by the FDA. In general, ARM would support FDA allowing for increased interactions with Sponsors during the TRG process and for the FDA to publish a more detailed summary on the rationale for each TRG classification recommendation. This detailed public summary on the rationale for the TRG classification recommendation should be explicit as to why the particular HCT/P was considered, or not, for homologous use. This additional clarity will increase predictability and will be beneficial to the field. We acknowledge FDA's assertion that TRG recommendations are non-binding and should not be perceived as precedent. However in the absence of another, better source of "current Agency thinking" industry's only option is to attempt to interpret current Agency thinking and act upon TRG recommendations. Thus, it would be very useful if the TRG webpage where the recommendations are published were to be updated at least once every quarter.

III. QUESTIONS AND ANSWERS

1. 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 that may not be identical to the donor's cells, or recipient tissues that may not be identical to the donor's tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.[3]

[2] Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Docket. No. 97N-0068 (February. 28, 1997) page 19. http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm062601.pdf.

[3] "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26749 (May 14, 1998).

1-1. 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.

1-2. Pericardium is intended to be used as a wound covering for dura mater defects. This is homologous use because the pericardium is intended to repair or reconstruct the dura mater and serve as a covering in the recipient, which is one of the basic functions it performs in the donor.

Generally, 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.[4]

ARM Comment #4: The Alliance for Regenerative Medicine believes FDA should delete the sentence "Generally, 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" as it is not clear and might cause confusion with Industry. Alternatively, if the Agency wishes to keep the sentence, we recommend the following rewording: "Generally, if an HCT/P is intended for an unproven therapeutic use, the HCT/P is likely not intended for homologous use only[4]". In this case, it may be necessary to define "unproven".

2. 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.[5] 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 homologous uses to be 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. 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.

ARM Comment #5: The Alliance for Regenerative Medicine believes additional and more detailed examples should be cited in this section, both positive and negative, in particular where "repair, reconstruction and supplementation" are accomplished using donor tissue that is from a different anatomic location than the repair site in the recipient. One example, drawn from a TRG recommendation is: "Allogeneic mineralized or demineralized cortical human bone for use in orthopedic repair, replacement and reconstructions applications for filling or augmenting bony voids or gaps involving the extremities, cranium, and spinal column and for augmentation for posterior lateral fusions in the spinal column". This was considered homologous use. Providing more details as to why this was considered homologous use would be helpful. Additionally, it would be helpful for the Agency to clarify further the difference between "physical" and "mechanical" restoration of tissues (see first sentence in this section) or delete these terms to avoid potential confusion and limit wording complexity.

3. What does FDA mean by "the same basic function or functions" in the definition of homologous use?

For the purpose of applying the 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

[4] "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" 66 FR 5447 at 5458 (January 19, 2001).

[5] "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 regulated solely under section 361 of the PHS Act, provided the HCT/P meets all the criteria in § 1271.10, including minimal manipulation and homologous use."

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.

A homologous use for a structural tissue would generally be to perform a structural function in the recipient, for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion.

A homologous use for a cellular or nonstructural tissue would generally be a metabolic or biochemical function in the recipient, such as, hematopoietic, immune, and endocrine functions.

ARM Comment #6: The Alliance for Regenerative Medicine believes it would be helpful for the FDA to provide additional clarity on the above two sentences. Since in the previous final regulations (““Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” 66 FR 5447 at 5458 (January 19, 2001)”, FDA explicitly chose to eliminate the distinction between structural and non-structural tissues and cells from the definition homologous use, it would be helpful to explain why FDA believes now that these rebuttable presumptions regarding structural vs non-structural tissues and cells are appropriate. Alternatively, ARM’s recommendation would be to delete these two sentences.

3-1. The basic functions of hematopoietic stem/progenitor cells (HPCs) include to form and to replenish the hematopoietic system. Sources of HPCs include cord blood, peripheral blood, and bone marrow.[6]

a. HPCs derived from 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 derived from bone marrow are infused 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. A manufacturer provides HPCs derived from cord blood with a package insert stating that cord blood may be infused intravenously to differentiate into neuronal cells for treatment of cerebral palsy. This is not homologous use because there is insufficient evidence to support that such differentiation is a basic function of these cells in the donor.

3-2. The basic functions of the cornea include protecting the eye by forming its outermost layer and serving as the refracting medium of the eye. A corneal graft is transplanted to restore sight in 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.

3-3. 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.

3-4. The basic functions of amniotic membrane include covering, protecting, serving as a selective barrier for the movement of nutrients between the external and in utero

[6] Bone marrow meets the definition of an HCT/P only if is it more than minimally manipulated; intended by the manufacturer for a non-homologous use, or combined with certain drugs or devices.

environment, and to retain fluid in utero. 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.

3-5. 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.

ARM Comment #7: The Alliance for Regenerative Medicine believes the definition provided in this draft Guidance Document does not consider the "same basic function" in a way that is consistent with the Preamble that says "what the tissue does from a biological/physiological point of view, or is capable of doing when in its native state."(63 Fed. Reg. at 26749) and should address and explain this departure from Preamble.

4. 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.[7] 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.

4-1. 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 provides a supportive layer of the integument and protects the body from mechanical stress.

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.

4-2. The basic functions of amniotic membrane include serving as a selective barrier for the movement of nutrients between the external and in utero environment and to retain fluid in utero. An amniotic membrane product is used for wound healing of dermal ulcers and defects. This is not homologous use because wound healing of dermal lesions is not a basic function of amniotic membrane.

ARM Comment #8: Paragraph 4-2 appears inconsistent with Paragraph 3-4, which acknowledges that the basic functions of amniotic membrane also include covering and protecting. These functions specifically are included in the definition of "repair," which is a recognized homologous use. Consistent with Paragraph 3-4, we recommend the list of basic functions of amniotic membrane in 4.2 be expanded to include "covering and protecting". This may modify the conclusion on homologous use made in paragraph 4-2.

4-3. The basic functions of pancreatic islets include regulating glucose homeostasis within the body. Pancreatic islets are transplanted into the liver through the portal vein,

[7] "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" 66 FR 5447 at 5458 (January 19, 2001).

for preservation of endocrine function after pancreatectomy. This is homologous use because the regulation of glucose homeostasis is a basic function of pancreatic islets.

ARM Comment #9: The Alliance for Regenerative Medicine would recommend the FDA add another sub-section in this Section, i.e. add Section 4-4, to define in detail how homologous use applies to HCT/Ps intended for wound healing. We believe Industry would benefit from both positive and negative examples of "same basic function or functions" in this context.

5. 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.[8] 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).[9]

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).

6. 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 the circumstances that the HCT/P is, with the knowledge of the manufacturer or its representatives, offered for a purpose for which it is neither labeled nor advertised.

[8] "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" 66 FR 5447 at 5458-5459 (January 19, 2001).
[9] *Id.*