A couple of issues to address are 'homologous' use and 'minimal manipulation'. Everybody has their own definition for 'homologous' use and 'minimal manipulation' as it fits their purposes, however the only definition that counts in the human biologics' world is the definition listed by the FDA in the December 2017 Final Guidelines for Title 21 of the CFR (Code of Federal Regulations) Part 1271.10 (a) 1 criteria of minimal manipulation and 21 CFR 1271.10 (a) 2 criterion of homologous use. Is should be noted that these guidelines supersede the Adipose Draft Guidance that has now been officially withdrawn.

Minimal Manipulation: *HCT/P (Human cells, tissues, and cellular and tissue-based product)*

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).

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.

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

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);

• Lymph nodes and thymus

• Parathyroid glands;

• Peripheral nerve; and

• Pancreatic tissue.

> *Note: Cord Tissue, ie. Wharton's Jelly, is a structural tissue and falls into the same category as adipose tissue. This is important to note because the FDA gives examples of minimal vs more than minimal manipulation of adipose tissue, ie. Structural tissue, ie. Cord Tissue Note: Cord Blood is a non-structural tissue*

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.*If you look at this question closely you will see that they are saying that if a manufacturer processes structural tissue and removes the cells, you are left with a decellularized extracellular matrix that is considered more than*

minimally manipulated because the processing altered the original relevant characteristics of the structural tissue relating to its utility to provide cushioning and support. It did NOT make any differentiation as to HOW the cells were removed or the function of the cells that have been removed. The question is, can the left-over product after processing of cord tissue still function as structural support for the umbilical cord and act as a conduit?

> *In the case of Cord Tissue (Wharton's Jelly), the argument is made that it is used to cushion and or support the joint. If that is the case, then the actual structural tissue itself must be injected into the joint, not just the cellular components removed from the cord tissue. As noted in part 2 of Example 14-1 listed below, elimination of the surrounding structural components that provide cushioning and support from the structural tissue is considered MORE than minimal manipulation because it is altered from the original relevant characteristics.*

Another Example:

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.

> *Based on the above FDA example, it made no difference whether the structural tissue was enzymatically digested or mechanically disrupted. The end product was **more** than minimally manipulated because the original relevant characteristics (structural support of the intimal layer of the umbilical cord in order to act as a conduit), were eliminated and could no longer function as the original structural tissue functioned.*

By contrast, there is no question by any regulatory authority that centrifuge processing of the cord blood, resulting in removal of the RBC's and HLA-DR components, IS considered minimal manipulation.

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.*

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.

*Note that in order to fall under homologous use, the cellular or structural component must perform **any, not all,** of the defined functions of the cellular or structural component.*

In order to determine whether not a structural tissue in being used in a homologous manner, we first must know the definition of the function of the structural tissue.

"The **umbilical cord** connects the placenta to the fetus with two smaller arteries, and one large **vein**. As the **cord** grows, the vessels tend to spiral.

Wharton's jelly, a gelatinous substance **inside the umbilical cord**, helps protect the vessels and prevents the **cord** from kinking"

https://quizlet.com/24512036/respiratory-therapy-244-final-exam-ch2-flash-cards/

***The FDA listed multiple examples of <u>acceptable</u> homologous use of structural tissue**:*

Heart valves transplanted to replace a heart valve (same function)

Pericardium used to cover dura mater (acts as a covering)

Amniotic membrane applied to the surface of an eye (acts as a covering)

Adipose tissue to fill voids in the hands or face (acts to support the tissue)

Adipose tissue for breast reconstruction/augmentation (acts to cushion or support)

They also listed multiple <u>unaccepted</u> homologous use of structural tissue:

Amniotic membrane for wound healing (wound healing is not a basic function of amniotic membrane)

Amniotic membrane for bone tissue replacement (bone regeneration is not a basic function of amniotic membrane)

Adipose tissue to treat neurological conditions (limiting autoimmune reaction and promoting re-myelinization is not a basic function of adipose tissue)

Adipose tissue to treat musculoskeletal conditions (regenerating or promoting regeneration of cartilage or tendon is not a basic function of adipose tissue)

None of the above examples given by the FDA delineated whether or not the structural tissue was processed, because that would deal with minimal manipulation.

The above examples are as to whether or not the structural tissue is acting in a homologous manner (the original function of the structural tissue in the body). The question then becomes……is the original function of cord tissue designed to support and cushion the cord or is its function to protect and act as a conduit to prevent kinking in the cord?

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.

The cellular component derived from umbilical cord blood contain a small concentration of hematopoietic stem cells (CD 34+), along with Regulatory T-cells (CD45RA+ which stimulate T1 and T2 helper cells), Mesenchymal Stem Cells (CD 90) which are primarily anti-inflammatory and immune-regulatory in allogeneic CB cells, Progenitor Cells, Mononuclear Cells (MNC'S), and Immune Regulatory Cells.

Crit Rev Oncol Hematol. 2011 Aug;79(2):112-26. doi: 10.1016/j.critrevonc.2010.07.009. Epub 2010 Aug 19.

Immune regulatory cells in umbilical cord blood and their potential roles in transplantation tolerance.

Kim YJ[1], Broxmeyer HE.

Simply put. Cord Blood derived cells fall directly under the categories of Minimal Manipulation AND Homologous use, as defined by the above FDA Guidelines whereas, Cord Tissue falls OUT of both Minimal Manipulation AND Homologous Use.

By definition, cord blood cells DO fall into the homologous use category.

Discussions of 'minimal manipulation' and 'homologous use' are definitely important topics to discuss, but only in the context of the actual FDA Guidelines. Other than the italicized comments, all of the content was taken from the referenced: ***Guidance for Industry and Food and Drug Administration Staff***

Highlights and italicized comments added

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

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 Corrected December 2017