

The FDA Provides New Guidance on the “Minimal Manipulation and Homologous Use” of Cell and Tissue Products.

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The Food and Drug Administration (FDA) recently issued a set of regulatory guidelines setting forth their thoughts on:

- The criterion for minimal manipulation and
- The criterion for homologous use of human cells, tissues, and cellular and tissue-based product (HCT/P): The guidelines should help stem cell and tissue manufacturers, healthcare providers, and FDA staff.

The definitions of these terms are critical factors in determining whether a product is more than minimally manipulated. Exceeding the minimal manipulation threshold and the homologous use standard can mean millions of dollars. Products that exceed the minimally manipulated threshold (or the homologous use test) are generally required to apply seek approval from the FDA as a drug. This means the manufacturer will need to spend time and money:

- Applying for an IND (Investigational New Drug Application)
- Conducting clinical trials
- Investing a lot of money
- Taking 10-15 years for final approval

HOPING TO TAKE ADVANTAGE OF THE NEW MEDICAL POSSIBILITIES WITH STEM CELL THERAPIES? BE INFORMED.

The FDA has developed new guidelines that expand the safety requirements and manufacturing standards for stem cell treatments.

Background

The FDA 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. The FDA authority for regulating human cell and tissue products is based on the Federal, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act).

“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. “

PHYSICIAN STEM CELL THERAPIES LEGALLY AMBIGUOUS, WHILE REGENERATIVE CLINICS PROSPER

Recent press calls into question widespread “regenerative” and anti-aging medicine, and physician practices that use stem cell therapies.

The FDA has the authority to define and regulate HCT/Ps as drugs, biological products, or medical devices using a tiered, risk-based approach which was implemented by the FDA in 2005. HCT/Ps that meet specific criteria or fall within detailed exceptions do not require premarket review and approval.

The FDA considered the following factors in the development of its tiered, risk-based approach (commonly called the “tissue rules”):

- 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
- How clinical safety and effectiveness can be assured

DOES FDA DEEM MY PRODUCT TO BE A MEDICAL DEVICE?

Does FDA deem your product to be a medical device, or is it just a consumer product that would not be regulated by FDA? Here are basic steps you can take to work through the puzzle.

When HCT/Ps qualify for the FDA exceptions

HCT/P Products will be regulated as a drug, device, and/or biological product pursuant to the FD&C Act (or the PHS Act) – and will require premarket approval – unless the product meets all following conditions:

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
4. Either:
 1. 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
 2. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 1. Is for autologous use;

2. Is for allogeneic use in a first-degree or second-degree blood relative; or
3. Is for reproductive use.

The new guidelines are in response to numerous requests for guidance as to what these definitions mean.

The minimal manipulation standard

The FDA defines minimal manipulation as:

- 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;
- For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

The homologous use standard

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).”

The FDA position is that it will look at the intended use of the HCT/P based on:

- Labeling
- Advertising
- Other manufacturer intent indicators

This means companies involved with making and developing HCT/P products should be especially careful about how they promote their products. An experienced FDA HCT/P lawyer can help will review your marketing and promotional materials along with the evidence needed to qualify for exception to a drug/device/or biological product classification.

Key features of the new guidelines for HCT/P products

Some of the many useful features, of the new FDA guideline, according to Stem Cell Assays, include:

- A helpful feature is the inclusion of a Questions and Answers section – with numerous examples and explanations of confusing issues. It’s the bulk of the document.
- The difference between structural and non-structural tissues is explained
- The discussion of adipose tissue – a *“highly controversial and poorly understood type of HCT/P,”* is explained.
- The FDA considers the default position to be “more than minimally invasive,” which means manufacturers and others have the burden of showing their product is minimally invasive.
- The guidance document will be modified after comments from readers are analyzed.

A few of the Q and As

Question: Why is there a different definition of minimal manipulation for structural tissue and for cells or nonstructural tissue?

Answer: Under the regulations, HCT/Ps are considered either structural tissues or cells/nonstructural tissue, based on the characteristics of the tissue in the donor...Structural HCT/Ps generally raise different safety and efficacy concerns than do cells or nonstructural tissues.

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

Answer: 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.

Question: What if the HCT/P provides dual functions?

Answer: HCT/Ps may perform multiple functions and the 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.

Question: If my HCT/P is a structural tissue, how do I determine whether it is minimally manipulated?

Answer: 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.

There are many more useful Qs and As in the new guidance document

Examples from the new FDA minimal manipulation and homologous use guide

Examples of structural tissue and cells or nonstructural tissues are provided in the document.

Two of the example Q and As are:

Example 1. 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
- Tendon or ligament

Example 2. 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*
- *Pancreatic tissue.*

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

Regulatory scope and additional information

There are exceptions to these FDA requirements. For example,

- There are surgical procedure exceptions.
- There are exceptions for products that don't meet the CFR definition of HCT/P. 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 the Code of Federal Regulations (CFR) because it is a blood product.

FDA compliance consideration considering new guidance regulation

The FDA, to give manufacturers time to submit an IND or marketing application after reviewing the new guidance document, states it will be using enforcement discretion during the first 36 months following the issuance of the guidance document – unless there are reported safety concerns or safety concerns that are potentially significant.

In response to numerous questions about the FDA rules on when human cell and tissue products qualify for an exception for the need to seek approval as a drug, biological product, or medical device – the FDA recently announced new guidelines. These guidelines will be amended after a sufficient review period.

The guidelines seek to answer many questions including when HCT products meet the minimal manipulation and the homologous use steps. HCT/PS that don't qualify for an exception will need to be approved as IND for drugs or will need to meet the FDA approval requirements for medical devices and biological products.

Contact Cohen Healthcare Law Group, PC to speak with an experienced FDA healthcare & FDA lawyer regarding compliance and regulatory issues surrounding your regenerative or stem cell medicine or healthcare products.

Contact our healthcare law and FDA attorneys for legal advice relevant to your healthcare venture.