You Can't Put That Tissue There: FDA Clarifies Important HCT/P Regulatory Criteria

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One of the first warning letters of 2018 was issued to a manufacturer of a human cell, tissue, and cellular and tissue-based product (HCT/P) that the Food and Drug Administration said was regulated as a drug, and as a biological product, and required a biologics license because it did not meet the definitions of minimal manipulation and homologous use.[1] The meanings of these two terms are the subject of a new guidance FDA issued in November 2017. The guidance, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use* (Guidance), provides clarification on these two criteria that are used to determine how an HCT/P will be regulated by FDA.[2]

FDA also issued another HCT/P guidance, *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*, which covers another HCT/P regulatory exception, at the same time.[3] We are not covering the Same Surgical Exception guidance in this article. Because both guidances cover various aspects of adipose tissue regulation, the agency withdrew the previous adipose tissue draft guidance titled: *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations*. Adipose tissue regulation will be discussed in more detail below.

Background

HCT/Ps are biologic products typically regulated by the Center for Biologics Evaluation and Research (CBER). FDA's regulatory authority over HCT/Ps stems from both the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act (PHSA). Some HCT/Ps do not require premarket approval and are regulated only under section 361 of the PHSA and 21 CFR Part 1271. In order to avoid regulation as a new drug requiring premarket approval, an HCT/P in this category must meet all of the following criteria:

1. The HCT/P is minimally manipulated (see below for how FDA defines this phrase);
2. The HCT/P is intended only for homologous use;
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:
   - 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
   - The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
     - Is for autologous use;
     - Is for allogeneic use in a first-degree or second-degree blood relative; or

1 https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm591225.htm
2 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
3 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf

- Is for reproductive use.[4]

HCT/Ps that do not meet all the criteria above may require approval of a new drug application (NDA) or biologics license application (BLA) in order to be lawfully marketed.

Guidance

The Guidance provides clarification on the first two criteria: minimal manipulation and homologous use. The Guidances also provides an overview of FDA's HCT/P enforcement policy. Before a minimal manipulation determination can be made, the HCT/P must be classified as either structural tissue or cellular/nonstructural tissue. This classification is based on the characteristics of the HCT/P in the donor before recovery and processing.

Minimal Manipulation
Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues. The Guidance provides the following as examples of structural tissues:

- bone,
- skin,
- blood vessels,
- articular cartilage,
- adipose tissue, and
- tendons.

Adipose tissue has several purposes, including energy storage and insulation, but for the purpose of applying the HCT/P regulatory framework, FDA considers it to be a structural tissue. When evaluating whether processing of adipose tissue meets the regulatory definition of minimal manipulation, manufacturers should consider whether the processing alters the original relevant characteristics of the adipose tissue, which relate to its utility to provide cushioning and support

Cells or nonstructural tissues, on the other hand, serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions. Lymph nodes, reproductive cells and tissues, pancreatic tissue, and peripheral nerves are all examples of cells or nonstructural tissues.

The minimal manipulation analysis for both categories turns largely on how the HCT/P is processed. Processing is broadly defined as "any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution."[5] Testing for microorganisms, preparation, sterilization, culturing, decellularization, and preservation for storage are all forms of processing.

Structural tissue is minimally manipulated if the processing does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.[6] For example, shaping bone to form a pin would be considered minimal manipulation because the processing does not alter the bone's original relevant characteristics relating to its utility to support the body and protect internal structures. However, bone treated with acid so it forms a gel would be 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.

The Guidance contains several other examples that may be useful in analyzing a particular process, including how demineralized bone matrix products will be treated. The Guidance also outlines how the removal of cells from structural tissue affects whether an HCT/P is minimally manipulated. If the processing of a structural tissue alters the cellular or extracellular matrix components without altering the original relevant characteristics of the tissue, then the tissue will

4 21 CFR 1271.10(a)
5 21 CFR 1271.3(ff)
6 21 CFR 1271.3(f)(1)

typically be considered minimally manipulated. For example, a manufacturer processes skin to remove epidermis, and freeze-dries and packages the remaining connective tissue as decellularized dermis. This product would generally be 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.

Similarly, cells or nonstructural tissues are considered only minimally manipulated if the processing of the product does not alter the relevant biological characteristics.[7] For this purpose, FDA considers biological characteristics to include differentiation and activation state, proliferation potential and metabolic activity. For example, culturing hematopoietic stem/progenitor cells to produce terminally differentiated cells would be more than minimal manipulation because the processing alters the cells' relevant biological characteristics of multipotency and capacity for self-renewal.

Homologous Use
The Guidance also provides clarification of the homologous use requirement. 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 it did in the donor*.[8] For example, a heart valve from a donor that is used to replace a diseased heart valve in a recipient is considered homologous use because the heart valve is performing the same function. On the other hand, adipose tissue, commonly referred to as body fat, which is used to treat neurological disorders by limiting autoimmune reaction is not a homologous use because limiting immune reaction is not a basic function of adipose tissue in the donor. Again, the Guidance provides additional examples.

Enforcement Policy
FDA also set forth its current enforcement policy in the Guidance stating that it intends to exercise risk-based enforcement discretion for the first 36 months following the issuance of the Guidance to allow manufacturers that do not meet all the criteria of 21 CFR 1271.10(a) to submit the requisite marketing applications. FDA intends to focus its enforcement actions on products that use riskier routes of administration, such as intravenous injection, aerosol inhalation, and central nervous system infusion. HCT/Ps intended for non-homologous use in the treatment of serious and/or life-threatening diseases or conditions will also be an enforcement focus.

Warning Letter

In January 2018, FDA issued a warning letter to a manufacturer of an HCT/P that the agency said required premarket approval as a drug because the product failed to meet the criteria for minimal manipulation and homologous use. The company processed a structural tissue that is expanded through cell culture into an autologous product intended to treat conditions such as anoxic brain injury, Parkinson's disease, amyotrophic lateral sclerosis, stroke, and multiple sclerosis. FDA found that both processing and expansion of the HCT/P constituted more than minimal manipulation because they each altered the original characteristics of the product.

Additionally, FDA also claimed that the company's own records showed that its HCT/P was intended to treat numerous diseases and conditions, including stroke and multiple sclerosis, meaning the product was not intended to perform the same basic functions of the original tissue (to provide cushioning and support), and was not intended for homologous use. FDA also cited the company's Chief Operating Officer as saying its products are "breakthrough technologies which are about sending cells the same way you send any other drug to a doctor." FDA characterized this language as the company itself promoting the product as a drug, not an HCT/P. Because the product failed to meet the relevant criteria for regulation solely under 21 CFR Part 1271 and section 361 of the PHSA, and didn't fall under any of the exemptions to regulation, FDA concluded it should be regulated as a drug and as a biological product.

FDA also noted several CGMP deviations, including failure to assure a system was in place to monitor environmental controls to prevent contamination during aseptic processing, and failure to establish and follow a written testing program designed to assess the stability characteristics of the products. In response to FDA's inspection findings listed in Form FDA 483, the company had contended that the product is for research use only and is properly labelled as such. The

7 21 CFR 1271.3(f)(2)
8 21 CFR 1271.3(c)

company asserted that the product is being investigated in a safety study approved by an Institutional Review Board (IRB) and is not commercially-distributed. In the Warning Letter, FDA explained that an Investigational New Drug (IND) must be in place for the product in order for the company to lawfully distribute it for research purposes.

AGG Observations

1. Companies should be mindful of how they describe their products both orally and in written documentation. Products that cannot be legally marketed as drugs should not be described in comparison to drugs. As shown by the Warning Letter, FDA may use a company's statements made about a product as evidence that the product is intended to be marketed as a drug and requires marketing authorization.
2. Even if a research product is used only in an IRB-reviewed and approved study, an IND is still required. IRB approval alone is not a substitute for an IND and, in any event, an IRB is likely, in many cases, to want an IND. Additionally, the statement "for research use only" does not shield a product from FDA regulation.
3. Although FDA has issued an enforcement policy in this guidance, companies should keep in mind that such a policy is not binding on FDA. FDA may decide in a particular case that exercising enforcement discretion is not appropriate, particularly if a safety issue arises.

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