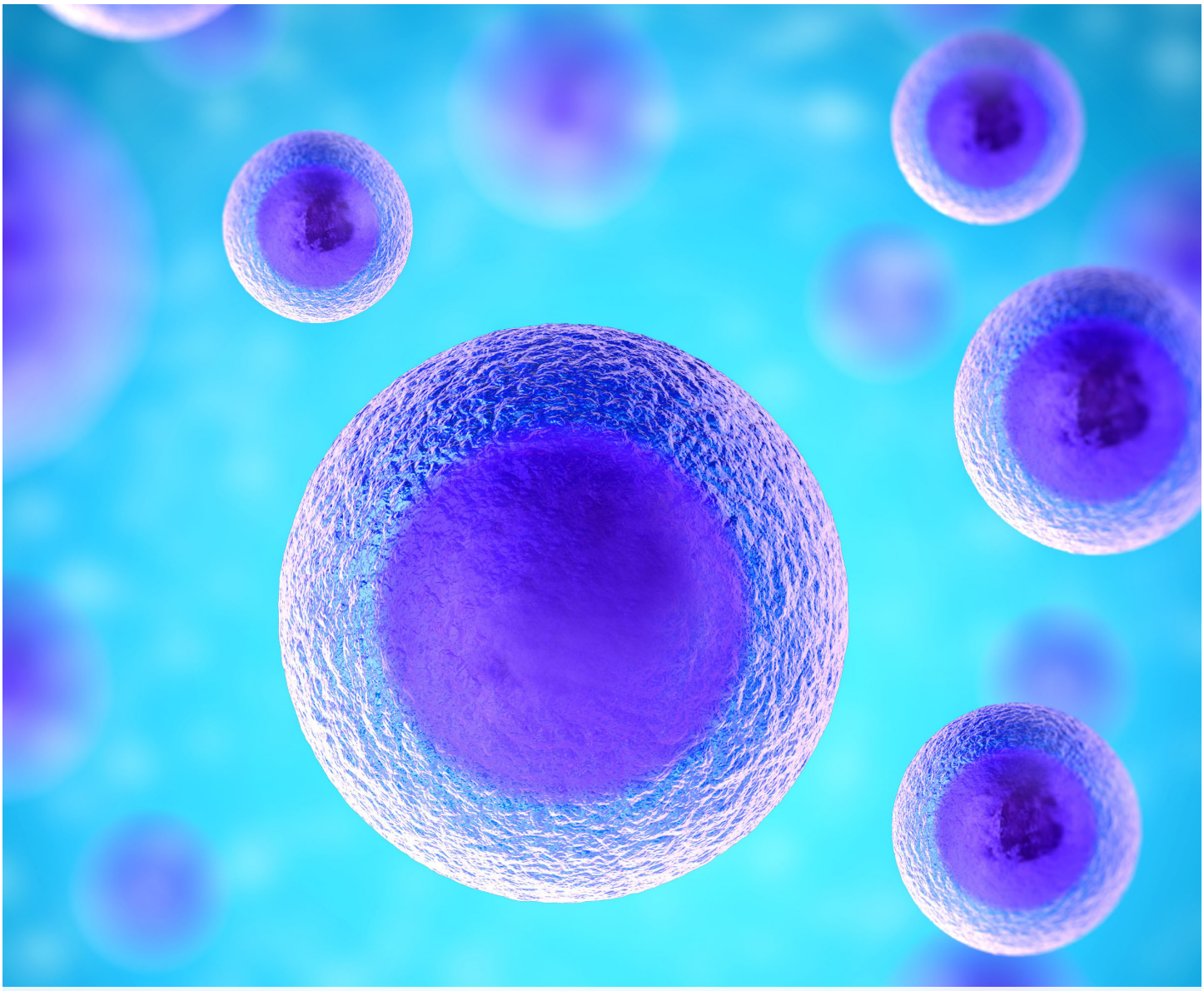

Addressing the Challenges of Human Tissues and Cell Products Regulation

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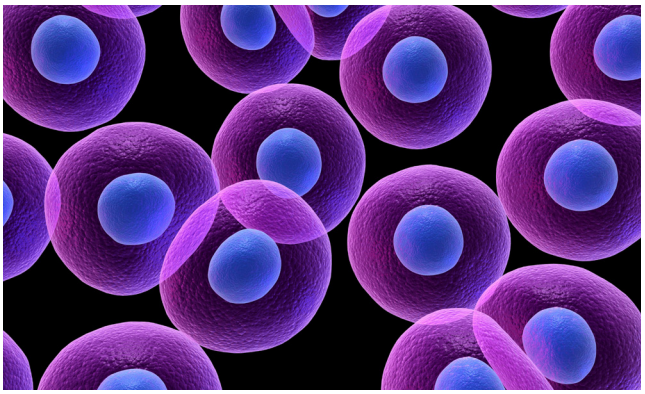


Regulatory oversight of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) is complicated. This white paper highlights what sponsors, investigators and IRBs need to know about how these distinct products are regulated.

Introduction

Clinical investigations to gather data to support new drug, biologic, and device approvals generally require the protocol and other documents to be submitted to the FDA prior to starting the trial. In contrast, Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) have a distinct regulatory classification from drugs, biologics, and devices, and those that meet specific regulatory criteria can be studied in clinical investigations without prior FDA review as long as there is appropriate Institutional Review Board (IRB) oversight. While the sponsor should interpret the regulatory language and make the determination regarding whether an FDA submission is required in these cases, the burden is on the reviewing IRB to ensure that the regulatory requirements are being met appropriately.

Due to the details of the regulations for HCT/Ps, determining whether or not a given clinical investigation of a product requires prior FDA review can be complicated. If the sponsor provides the necessary information for the IRB to confirm the sponsor's assessment of the regulatory classification in the IRB submission, it will increase the efficiency of a high-quality review, and ensure that the study will be in compliance for possible FDA inspection later.

Background

The definition of an HCT/P is established in the regulations[1] as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." In the regulations, this definition is followed by two lists; a list of examples of products that are considered HCT/Ps, including stem cells from peripheral and cord blood and bone, and a numbered list of products that are not considered HCT/Ps, including blood components and bone marrow for homologous use (in certain situations). The similarities in the examples of products that are and are not considered HCT/Ps points to the difficulties in classification. Many products commonly considered to be HCT/Ps are not on either list, such as products from chorion or amnion, further requiring close attention to the regulatory classification.

21 CFR Part 1271,
Human cells, Tissues, and Cellular and Tissue-Based Products,
Subpart A, General provisions, § 1271.3:

"d) Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. 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 parts 607 and 207 of this chapter, 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;

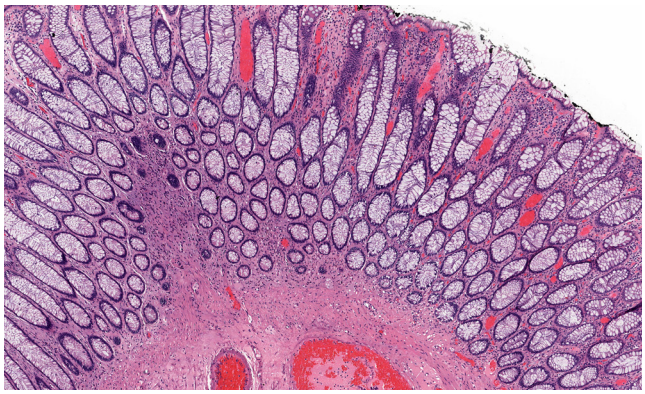
(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in 809.3(a) of this chapter.

(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."

FDA takes a risk-based approach to regulate these products through significantly different pathways. If the HCT/P does not meet a set of specific requirements, the HCT/P is regulated as a device or biological product. This means FDA premarket approval – including the requirement for FDA review prior to starting a clinical investigation – is required. On the other hand, no premarket approval is required for a HCT/P that meets these requirements, and no FDA review is required prior to starting a clinical investigation. Those products are subject only to regulation under section 361 of the Public Health Service Act (42 USC 264), referred to as a "361 HCT/P".[2] The unified system for listing the HCT/Ps requirements and for registering HCT/Ps establishments is found in the regulations at 21 CFR § 1271.[3]

The requirements listed in those regulations include five parts, each with specific elements. Therefore, a determination of which products require FDA review is made by analyzing each of these regulatory requirements in 21 CFR 1271: minimal manipulation, homologous use, manufacturing and storage agents, systemic effects, and registration. Because of the lack of clarity around most of the requirements, IRBs analyzing their use require specific product information and knowledge to assure proper analysis.



The definition of an HCT/P is established in the regulations as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."

Requirements

The IRB must have certain information in order to assess each of the five requirements in 21 CFR 1271.10(a). Again, if the product being tested meets these five requirements, FDA review of the product is not required. Only one requirement—manufacturing registration—is easily verified. In contrast, the other four requirements necessitate significant analysis. Understanding the requirements and the parameters of each of those analyses provides a useful outline to ensure that sponsors and investigators provide the appropriate information in their IRB applications and protocol documents.

A. Minimal Manipulation

The first requirement is that the product must be "Minimally manipulated,"[4] which is defined in the regulations based on the tissue:

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; and

2. For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues" [5]

The first step is therefore to determine whether the main function of the HCT/P in the donor is structural or not. Of note, structural tissue can be composed of both structural components (such as collagen or hydroxyapatite) and cells. If cells are part of the structural tissue included in this criterion, removing those cells can be considered more than minimal manipulation.

B. Homologous Use

The second requirement is that the product must be intended for homologous use only. This means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues is being performed with an HCT/P that performs the same basic function in the recipient as in the donor. This can follow from the prior structural/ non-structural separation but requires a different analysis as it focuses on the use of the cells.

When HCT/Ps are marketed, the limitation to homologous use needs to be "reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." [6] In the research setting, this means that the specific use of the product for the trial must match the same basic function, and the objectives of the research must be for the research to show that the product performs the same basic function. If a study is designed to test if a cellular product does more than perform the same basic function in the recipient, this requirement would not be met.

C. Manufacture

The third requirement involves manufacturing. [7] The manufacture of the HCT/P cannot involve the combination of the cells or tissues with another article, such as a drug. Water, crystalloids, or a sterilizing, preserving, or storage agent are allowed provided that the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P. The amount, kind, and history of use of the additional article impact this assessment.

Unless the HCT/P is manufactured under an IDE or IND,[8] the fourth requirement is that the HCT/P manufacturer must be registered with the FDA.[9] The agency maintains these registrations in a publically accessible database.[10] Documents included with the IRB submission should clearly identify the manufacturer so that the IRB can confirm if the manufacturer is properly registered.

D. Systemic Effects

The fourth criterion is more complicated. To meet it, the product must meet either of two sub-requirements. [11] The first sub-requirement is the simpler, that the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function. From IRB experience and a review of the literature, the vast majority of HCT/P products fall into this first category. The conclusion of systemic effect and dependence on metabolic activity might follow from a homologous use analysis, but not necessarily.

If the product does not meet the first sub-requirement and it does have a systemic effect, it must fit into one of the following specific use situations: autologous use, allogenic use in a first-degree or second-degree blood relative, or reproductive use.

Review and Analysis

Because of the complexity of the definitions and classifications of HCT/Ps above, combined with the rapid development of new HCT/Ps, sponsors, investigators and IRBs will require an understanding of how the regulatory requirements are actually applied. For example, the Tissue Reference Group provides clarification for specific products in a public listing. [12]

From the FY 2015 Update:

- A dehydrated chorioamniotic membrane in sheet form, used as a wound cover, is regulated as an HCT/P under section 361 of the PHS Act and 21 CFR 1271.

- A tissue product consisting of cryopreserved chorionic small sheets is more than minimally manipulated because the processing alters the membrane's original relevant characteristics, and therefore, is not regulated as an HCT/P under section 361 of the PHS Act.

In 2014, FDA provided two draft guidance documents on similar issues. The first draft guidance, on what constitutes minimal manipulation specifically notes that if information does not exist to show that the minimal manipulation[13] requirement is met, a HCT/Ps would be considered a biologic or device. The implication is that the default position is that prior FDA review is required.

The FDA draft guidance on HCT/Ps derived from adipose tissue provides further insight into minimal manipulation and homologous uses in two examples. In the first example, stromal vascular fraction (SVF) is created from processing adipose tissue.[14] The SVF is being studied in chronic inflammatory diseases, ischemic diseases, orthopedic procedures, a treatment for obesity, and other applications.[15, 16] The FDA guidance specifically addresses SVF processing. If that processing involves enzymatic or mechanical procedures for cell isolation, instead of merely

aliquoting, rinsing, removing macroscopic debris, and freezing, the processing would be more than minimal manipulation and therefore would need FDA review prior to being studied. In the second example, adipose tissue used for breast plastic surgery and augmentation by subcutaneous injection for re-shaping (structure) is not considered as homologous use, since "the primary function of breast tissue is producing milk."

Other Considerations

Depending on the study, study designs could include comparators that would also require consideration of other regulations. Products that could serve as a comparator or control arm for an HCT/P could include biologics, devices, drugs, or a combination of products. A study using a drug as a comparator would need to additionally follow the regulations under 21 CFR 312 for the clinical study of drugs, and a study using a device would follow the regulations under 21 CFR 812 for the clinical study of medical devices. A common issue for studies that compare HCT/Ps to 510(k) cleared devices is that the cleared device needs to either have been used in specific accordance with its labeling[17] or meet the non-significant risk definition and follow the requirements for an abbreviated IDE.[18] Additionally, devices used in the creation of the product (such as platelet rich plasma) may separately be subject to FDA device regulations.

With their shortened process to market, HCT/P products are reasonably studied in post-market research designs. All FDA-regulated clinical investigations require IRB review and informed consent of the subject, as well as documentation of consent or a waiver of documentation of consent.[19] Study designs that include collection of data from existing records would fall under these requirements, regardless of the impracticability of obtaining consent from the patients.

Conclusions

In a submission for IRB review, sponsors and investigators who believe that FDA review is not necessary for the cellular product should explicitly address the specifics of how the product fulfills each of the criteria under 21 CFR 1271.10, so that the IRB can confirm this conclusion. HCT/Ps may fall outside these specific requirements based on relatively small differences in processing and manufacture. A product classified as cellular tissue might have structural properties, and structurally-classified products might have cellular properties. The same tissue may or may not require prior FDA review depending on the labelling or specific use in a study. With the FDA guidance on minimal manipulation and homologous use pointing toward the default position that a product requires FDA review until proven otherwise, the rationale for the product meeting the criterion of being minimally-manipulated and for homologous use would especially benefit from a detailed description.

The issues around these products appear to be increasing in complexity as the science progresses. Following the leaps of creative scientific discovery, biotechnology's advances will continually outpace attempts to codify them. Matching the study of the product to the appropriate regulatory pathway provides regulators and scientists investigating new therapies with many challenges.[20] Despite the nuance and uncertainty, HCT/Ps deserve careful attention to maximize their promise while ensuring regulatory compliance. Clear and effective communication, with explicit rationales and an understanding of the regulatory framework, are the tools to ensure a high-quality, timely review by an IRB. Using these tools will accelerate the scientific advancement of human health, while ensuring that the risks of progress never outweigh the value of human life.

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