Overview
The University of Arizona allows use of stem cells for new and novel research with human subjects; but it must comply with federal, state, and University requirements.

Human cell and tissue products or HCT/Ps means human biological products including human stem cells. The FDA provides this explanation of what is and what is not an HCT/P:
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))

Regulatory Authority for oversight
The Federal Food, Drug, and Cosmetic (FDC) Act and the Public Health Service (PHS) Act give the Food and Drug Administration (FDA) the legal authority and responsibility to regulate biologics including human stem cells. The FDA is given authority over stem cell biological products and procedures under 21 CFR Part 1271. If the HCT/P fails any of the exceptions in 21 CFR 1271, then the FDA considers the product as an HCT/P and as a drug, device, and/or biologic.

In practical terms, this means that the FDA may require an IND or an IDE submission before any research begins. Clinical research involving stem cell-derived test articles is subject to FDA regulations at 21 CFR Parts 312 and 812, regardless of the source of funding. This research is also subject to FDA’s IRB and informed consent regulations at 21 CFR Parts 50 and 56.

The FDA has issued regulatory guidance supported in some cases by court decisions (e.g. US v. Regenerative Sciences Inc.), painting a clear picture that stem cell clinics in a general sense (as well as their products, devices, and procedures) are within its regulatory domain and their products can be defined as biological drugs. Furthermore, in 2012 and 2013 the FDA took numerous actions related to stem cell clinics, such as warning letter issued to a number of clinics.
Human cell and tissue products (HCT/Ps)

The FDA has draft guidelines that recommend how stem cells should be obtained and what degree of manipulation is acceptable without requiring a new therapeutic, biologic, or drug application (PHSA – Section 361). A product that meets these requirements is referred to as a “361 HCT/P”:

1. The HCT/P must be minimally manipulated after removal;
2. The HCT/P must be 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 cannot 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.

What is Minimal Manipulation of a HCT/P?

The FDA pays attention to altering the relevant characteristics of tissues or cells. The FDA’s reasoning begins with the assumption that any conversion of tissues or cells is not minimal unless demonstrated otherwise. The role of proving that a process is minimal manipulation therefore falls to anyone – a sponsor, a researcher, or institution – who wants to show that a product qualifies as a 361 HCT/P. If a biological product is defined as more than minimally manipulated it automatically leads that product to be defined as a biological drug subject to the full spectrum of drug regulatory oversight by the FDA.

The core requirements for processes that can be considered minimal manipulation of HCT/P are:

1) For structural tissue, processing does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement;
2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues. (21 CFR 1271.3(f)(1)).

**Case Study:**
The FDA compares two HCT/Ps derived from amniotic membranes. In one, the process converts the membranes into an HCT/P packaged as sheets; in the other the membranes become a powder. For the FDA, the first HCT/P could represent minimal manipulation because it retains the characteristics of the amniotic membrane (that is, “flat and fibrous”). The second product, however, goes beyond minimal manipulation by changing flat and fibrous into powder. The first HCT/P passes the first requirement to be a 361 HCT/P; the second product does not.

**Homologous Use**
Another key term in the stem cell clinical arena is “homologous use”. When applied to an HCT/P product, it means that the clinical use of that product must be highly consistent with (i.e. homologous to) the properties of the original tissue from which the product was made; if it is not homologous, even if minimally manipulated it will automatically be considered a 351 drug product. An example of homologous use would be the transplant of hematopoietic stem cells to treat a hematopoietic disorder. In that case, a blood-related product is used to treat a blood-related disease.

**Human Embryonic Stem Cells (hESC)**
In March 2009, previous restrictions for use of federal funding for human embryonic stem cells (hESC) derivation and research were removed and/or reduced by the President. In order to facilitate research using hESC, the National Institute of Health (NIH) created a Human Embryonic Stem Cell Registry listing those lines that are eligible for use in NIH funded research.

The NIH has updated and published “Guidelines for Human Embryonic Stem Cell Research” that offers a set of ethical standards for performance for research with hESC.

The State of Arizona, however, prohibits experimentation on any human fetus or embryos:

**Arizona 36-2302:**
A person shall not knowingly use any human fetus or embryo, living or dead, or any parts, organs or fluids of any such fetus or embryo resulting from an induced abortion in any manner for any medical experimentation or scientific or medical investigation purposes except as is strictly necessary to diagnose a disease or condition in the mother of the fetus or embryo and only if the abortion was performed because of such disease or condition.

Ineligible Research Involving hESC or Human Induced Pluripotent Stem Cells

1. Research in which hESC (even if derived from embryos donated in accordance with federal guidelines)
2. Research in human induced pluripotent stem cells (hiPSC) are introduced into non-human primate blastocysts.

3. Research involving the breeding of animals where the introduction of hESCs (even if derived from embryos donated in accordance with federal guidelines) or hiPSC may contribute to the germ line.

**Research with Adult Stem Cells**

Generally, the collection or derivation of human multi-potent and pluripotent stem cells from sources other than embryos does not involve the same issues as encountered with hESC and is subject to the guidance and regulations for sampling any tissue from human research subjects. The use of the cells, however, may raise ethical issues similar to those encountered with hESC.

**Institutional Biosafety Committee (IBC) Approval**

All research performed at the University of Arizona with biohazardous and/or recombinant material, including stem cells, must be registered with Research Laboratory Safety & Services and approved by the Institutional Biosafety Committee (IBC) ([http://orcbs.arizona.edu/biosafety/new-approval-holders/information](http://orcbs.arizona.edu/biosafety/new-approval-holders/information)). Contact RLSS for guidance and assistance. This approval is required prior to submission to the IRB for review.

**IRB Review Requirements**

The University treats HCT/Ps like all other FDA regulated products, cosmetics, foods, live organisms, etc., by conducting an assessment of the need for FDA review (IND or IDE) based on regulatory interpretation. Some common issues in these studies that could assist researchers and institutions in planning any HCT/P research are:

- It is important to understand which regulations apply to a particular HCT/P and why
- The requirements around “minimal manipulation” and “homologous use” require particular analysis
- In some cases, study documents (including the protocol and consent) should not include anything beyond the stated (i.e., homologous) uses of the product
- A commercially available HCT/P may be regulated differently if the use per protocol varies from the current commercial labeling

The following criteria apply concerning the requirement for IRB review of proposed research:

1. *In vitro* research involving stem cells from which the identity of the donor cannot readily be ascertained by the investigator is not considered to be human subjects research and is not subject to IRB review. This assumes that the investigator and research institution do not have access to private information related to the cell line and that the holder of the identifiable private information related to the cell line has agreed that such information will not be released.
2. Research involving cells that have already been derived and established, where the
donor may be identified, including cells that retain links (such as a code) to identifying
information, is considered to be human subjects research and is required to undergo IRB
review and approval.

**IRB approval**

Investigators can assist the IRB by providing the rationale that places the product’s conversion,
use, and activity within the requirements for 361 noted above. The rationale will assist the IRB
to two ends:

1. To confirm whether the 361 HCT/P category is appropriate (and so not require an IND or IDE
   submission); and
2. To ensure that the protocol and consent form make no claims beyond the product’s labelled
   (i.e., homologous) use. For a 361 HCT/P, the protocol and consent can include only
   statements consistent with a homologous use.

If the IRB has questions and cannot resolve whether the product falls under the exemptions for
minimal manipulation, the investigator will be required to receive confirmation from the FDA in
writing.

**Conclusion**

For any research of tissue or cellular-based products, it is important to understand the FDA’s
approach toward HCT/P regulation. A thorough analysis of all points in the HCT/P requirements
of CFR 1271 is crucial. For studies that involve a 361 HCT/P, and which will not be conducted
under an IND or IDE, the IRB submission should contain clear rationale for that categorization,
and the study documents should support a clear intent to study only homologous uses that are
in-line with the commercial labeling.

**References**


Regulation of HCT/Ps (1997)

Determining the need for an IND

Draft Guidance Document “Minimal Manipulation of Human Cells, Tissues, and Cellular and
Tissue-Based Products

Draft Guidance Document “Human Cells, Tissues, and Cellular and Tissue Based Products
(HCT/Ps) from Adipose Tissue: Regulatory Concerns”