Human Cell and Tissue Laboratory Establishment Checklist

A Practical Guidance® Checklist by
Clint Hermes and Heather Pearson, Bass, Berry & Sims PLC

Clint Hermes
Bass, Berry & Sims PLC

Heather Pearson
Bass, Berry & Sims PLC

This checklist outlines key regulatory considerations for attorneys with clients looking to establish a laboratory that grows or uses human cells and tissues for implantation, transplantation, infusion, or transfer into a patient. This checklist describes regulatory issues faced by entities establishing laboratories and how the U.S. Food and Drug Administration (FDA) expects them to address these issues.

For information on FDA regulation of human cell and tissue laboratories, see FDA Drug Regulatory Activity Tracker.

Preregistration and Prelisting Considerations

Will the Laboratory Grow or Use an HCT/P?

A human cell, tissue, or cellular or tissue-based product (HCT/P) is an article containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient. The FDA provides a helpful list of covered human cells, tissues, and cellular and tissue-based products on its website.

- **HCT/Ps include** bone, ligament, skin, dura mater, heart valves, corneas, 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. 21 C.F.R. § 1271.3(d).
- **HCT/Ps exclude** vascularized human organs for transplantation, regulated under Sections 216, 371–377, and 377E of the Public Health Service Act, 42 U.S.C. § 216, 42 U.S.C. §§ 273–274d, 42 U.S.C. § 274(f)-5; Sections 1102, 1106, 1138, and 1871 of the Social Security Act, 42 U.S.C. § 1302, 42 U.S.C. § 1306, 42 U.S.C. § 1320b-8, and 42 U.S.C. § 1395hh; Section 301 of the National Organ Transplant Act, 42 U.S.C. § 274e; and state law such as the Uniform Anatomic Gift Act; whole blood or blood components or blood derivative products, regulated under 21 C.F.R. pts. 207 and 607; secreted or extracted human products, such as milk, collagen, and cell factors (excluding semen); some forms of donated bone marrow not combined with another article; ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than human; in vitro diagnostic products; and blood vessels recovered with an organ intended for use in organ transplantation and labeled for use in organ transplantation only, all regulated as biologics, drugs, or medical devices. See 21 C.F.R. § 1271.3(d)(1)–(8).

If the Laboratory Will Grow or Use an HCT/P, Does the HCT/P Require FDA Premarket Approval?

Some HCT/Ps are regulated only under Part 1271 of the Public Health Service Act and do not require premarket approval. These HCT/Ps are sometimes called "361 HCT/Ps." Others are regulated as biologics, drugs, or medical devices, and are subject to applicable statutory and regulatory premarket approval procedures.

To be excluded from premarket approval, the HCT/P must meet the following four criteria:

1. **Is the HCT/P minimally manipulated?** HCT/Ps must only be minimally manipulated, meaning 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 for cells and nonstructural tissues, "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f).
2. **Is the HCT/P intended for homologous use?** HCT/Ps must be intended for homologous use, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent. 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 C.F.R. § 1271.3(c).
3. **Is the HCT/P combined with a drug or device?** An HCT/P is not regulated only under Part 1271 if it is combined with another drug or device (except for a sterilizing, preserving, or storage agent).
4. **Does the HCT/P have a systemic effect or is dependent upon the metabolic activity of living cells?** An HCT/P cannot have a systemic effect on the metabolic activity of living cells, or be dependent on such activity, *unless* the HCT/P is for autologous use, is for allogenic use in a first or second-degree relative, or is for reproductive use. Autologous use "means the implantation, transplantation, infusion, or transfer of human cells or tissues back into the individual from whom the cells or tissue were recovered." 21 C.F.R. § 1271.3(a).

If the HCT/P does not meet all of the above criteria, the HCT/P will be regulated as a drug, device, or biological product. These HCT/Ps are subject to the registration and approval regulations specific to drugs, biological products, or medical devices, while still being subject to the donor eligibility procedures and Current Good Tissue Practice procedures (subpart D) in subparts C and D of 21 C.F.R. pt. 1271.

1. **Examples of HCT/Ps that must obtain premarket approval as biologics or drugs:** cultured cells, including nerve, fibroblasts, keratinocytes, ligaments grown on synthetic membranes or combined with collagen or bone marrow; cultured nerve cells; lymphocyte immune therapy; gene therapy products; human cloning; human cells used in genetic material transfer therapy; and unrelated allogenic hematopoietic stem cells and donor lymphocytes for infusion
2. **Examples of HCT/Ps that must obtain premarket approval as medical devices:** corneal lenticules, preserved umbilical cord vein grafts, human collagen, and femoral veins intended as AV shunts

Does an Exception Apply?

Regardless of which Act an HCT/P itself is regulated under, some entities are nonetheless excluded from some, if not all, of Part 1271's requirements.

- **Entities that do not need to comply with the requirements of Part 1271:** (1) an establishment that uses HCT/Ps solely for nonclinical scientific or education purposes; (2) an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during a surgical procedure; (3) a carrier that accepts, receives, carries, or delivers HCT/Ps in the usual course of business as a carrier; (4) an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implementation, transplantation, infusion, or transfer within a facility; or (5) an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cells or tissue donor (21 C.F.R. § 1271.15(a)–(e))
- **Entities that do not need to register or list their HCT/Ps independently, but must otherwise comply with other applicable requirements of subpart B of 21 C.F.R. pt. 1271:** an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues or sending the recovered cells or tissues and sending the recovered cells or tissues to the registered establishment (21 C.F.R. § 1271.15(f))

Registration and Listing

Registration Timing

An entity regulated only under Part 1271, and not otherwise excluded, must initially register its establishment and update its registration annually.

- **Initial registration.** An entity must register within five days after beginning operations. 21 C.F.R. § 1271.21(a).
- **Annual registration.** An entity must update its registration annually in December. 21 C.F.R. § 1271.21(b).
- **Changes or amendments.** If the ownership or location of an establishment changes, or there is a change in the U.S. agent's name, address, telephone number, or email address, the registration must be amended within 30 calendar days of the change. 21 C.F.R. § 1271.26.

Registration Procedure

An entity must register through the FDA's electronic registration and listing system (eHCTERS). This same platform is used for the initial registrations and listings of HCT/Ps, annual registrations and listings of HCT/Ps, changes in any entity's information, or otherwise marking an entity inactive. The FDA provides detailed instructions on using eHCTERS on its website.

- Under some circumstances, electronic registration and listing requirements can be waived if the entity writes to the agency explaining why electronic submission is not reasonable. 21 C.F.R. § 1271.23(b).
- An entity should provide the registration number if the establishment is already registered with FDA as a blood, medical device, or drug establishment. If the entity already has a registration number, FDA does not give it a new registration number and the entity is not required to provide the physical location of the establishment, the mailing address of the reporting official, or the U.S. agent, if applicable. 81 Fed. Reg. 60170, 60223 (Aug. 31, 2016).
- All establishments should be independently registered.
- An entity should provide the legal name, street address including the postal code, and telephone number of the actual location of the establishment.
- An entity should provide the reporting official's mailing address including the postal code if it is different from the actual location of the establishment. The reporting official is the person appointed by the owner or operator to register the firm and answer all relevant correspondences and inquiries from the agency. The dated signature by the reporting official affirms that all information contained on the form is true and accurate, to the best of the official's knowledge.
- For non-U.S. entities only, an entity should provide the U.S. agent name, institution name if applicable, street address, email address, and telephone number. An agent must be a person residing or maintaining a place of business in the U.S. who a foreign establishment designates as its agent, and must be able to assist FDA in communicating with the foreign establishment, respond to questions about the products imported or offered for import, assist in scheduling inspections, and accept information and documents from the FDA if the agency cannot access the foreign entity.

Listing Timing

An entity regulated only under Part 1271, and not otherwise excluded, must initially list all HCT/P products the entity recovers, processes, stores, labels, packages, distributes, or for which it performs donor screening or testing.

- **Initial listing.** An entity must list all HCT/Ps within five days after beginning operations. 21 C.F.R. § 1271.21(a).
- **Changes or amendments.** After initially listing all HCT/Ps, an entity must update its listings at the time of change, or every June or December, whichever comes first after the change. 21 C.F.R. § 1271.21(c)(ii).

Listing Procedure

An entity must list and update its HCT/P products through eHCTERS. The listing must include all HCT/Ps, including the established name and the proprietary name, that the entity recovers, processes, stores, labels, packages, distributes, or for which it performs donor screening or testing; all HCT/Ps the entity began recovering, processing, storing, labeling, packaging, and distributing since the last listing period; all HCT/Ps the entity stopped recovering, processing, storing, labeling, packaging, and distributing since the last listing period; and all HCT/Ps that previously were discontinued but the entity resumed recovering, processing, storing, labeling, packaging, and distributing since the last listing period. 21 C.F.R. § 1271.25(b)–(c).

- An entity must indicate the activities performed by the registered establishment, such as recovering, testing, processing, labeling, screening, packaging, storing, or distributing.
- An entity must indicate if the HCT/P meets the four criteria necessary to be regulated solely under Part 1271. The platform includes a list of preprinted HCT/P types, but if the HCT/P type is not included in the

generated list, the entity should contact the agency's Tissue Registration Coordinator at tissuereg@fda.hhs.gov.

- An entity must indicate if the HCT/P is instead regulated as a drug, device, and/or biological product. The agency does not require establishments that manufacture drugs and devices under an investigational new drug application (IND) to register and list their HCT/Ps until the HCT/P is approved through a biological license application (BLA), a new drug application (NDA), a premarket approval application (PMA), or cleared through a premarket notification submission (510(k)).

Post-registration and Listing

FDA will assign each laboratory location a permanent registration number, though acceptance of an establishment registration and HCT/P listing does not constitute a determination that the establishment is in compliance with additional Part 1271 requirements, with any HCT/P license, or has been FDA approved. 21 C.F.R. § 1271.27. The following are additional post-registration compliance obligations or considerations.

Are Donors Eligible?

Establishments must screen and test HCT/P donors for risk factors for, and clinical evidence of, relevant communicable diseases. The entity must establish and maintain testing, screening, and eligibility procedures. See subpart C of 21 C.F.R. § 1271.

- A donor is only eligible if (1) screening shows that the donor is free from risk factors and clinical evidence of relevant communicable diseases, disease agents, or communicable risks associated with xenotransplantation, and (2) test results for relevant communicable diseases are negative or nonreactive. 21 C.F.R. § 1271.50.
- Donor eligibility determinations are not required when (1) there is an urgent medical need, (2) the cells and tissues are used for autologous use or allogenic use in a first or second-degree blood relative, (3) reproductive cells or tissues donated by a directed reproductive donor or a sexually intimate partner of the recipient, (4) cryopreserved cells or tissues for reproductive use that were for autologous use or donated by a sexually intimate partner of the recipient, or (5) when a cryopreserved embryo is used. 21 C.F.R. § 1271.90(a)–(b).
- All laboratories that perform required testing for HCT/Ps must be certified by CMS under the Clinical Laboratory Improvement Amendments (CLIA). 21 C.F.R. § 1271.80(c).
- The following records must be maintained for 10 years: (1) eligibility determinations for each HCT/P donor, (2) the results of an entity's procedures to prevent infectious disease contamination and cross-contamination during processing, and (3) English language translation of any required foreign-language records with a statement of authenticity from a translator. See 21 C.F.R. § 1271.55(d).

Are Current Good Tissue Practices (CGTPs) Being Followed?

Establishments must follow CGTP requirements, including those related to facilities; environmental controls; equipment; supplies and reagents; recovery, processing, and process controls; labeling controls; storage and receipt; pre-distribution shipments and distribution of HCT/Ps; and donor eligibility determinations, donor screening, and donor testing. 21 C.F.R. § 1271.150(b).

- An entity must have written standard operating procedures for donor infectious disease testing, donor screening, tissue quarantine, and preventing infectious disease contamination and cross-contamination during processing. 21 C.F.R. § 1271.180.
- If an HCT/P is regulated as a biologic, drug, or device, but the relevant biologic, drug, or device regulation conflicts with any regulation under Part 1271, the more specific regulation controls. 21 C.F.R. § 1271.150(d).

Is an FDA Inspection Required?

FDA is not required to conduct routine biennial inspections of manufacturers of 361 HCT/Ps. These inspections are based on priorities of each district. For HCT/Ps regulated as medical devices, biologics, or drugs, the applicable inspection regulations remain in effect.

Clint Hermes, Counsel, Bass, Berry & Sims PLC

Clint Hermes draws on his deep experience as general counsel at two teaching hospitals to advise clients on regulatory, accreditation, and corporate governance matters in academic medicine. In addition, Clint also offers clients practical advice and insights on all regulatory and contracting aspects of human and animal research.

Clint's accomplishments on behalf of academic medical centers have been as varied as negotiating complex academic affiliation agreements; implementing enterprise risk management programs; securing dismissal of a *qui tam* action involving federal grant compliance; preparing clients for Joint Commission, AAHRPP, and ACGME reviews; lobbying HHS for changes to a PREP Act declaration; obtaining a favorable OIG Advisory Opinion; and establishing healthcare and humanitarian programs overseas.

Clint has extensive experience with the regulation of human and animal research, clinical trial registration and transparency, conflicts of interest, federal grants, biospecimens, data sharing, and expanded access to investigational products. His work on behalf of the research missions of academic medical centers and life sciences companies has taken him throughout Africa, Asia, the Middle East, and South America. He has served on numerous Institutional Review Boards (IRBs) in the United States and abroad, including as Vice Chair of a Harvard-affiliated IRB and of a biobank IRB abroad, and as science policy advisor to a foreign government.

Clint has authored numerous articles and book chapters (including one published by Cambridge University Press) in the areas of international health projects and biomedical research and has been quoted in publications such as MIT's *Technology Review*, *Bloomberg Law*, *Modern Healthcare*, *STAT News* and Canada's *Globe and Mail*.

Before joining Bass, Berry & Sims, Clint experienced first-hand the unique needs of academic medical centers with large research programs and a global reach. He served as Senior Vice President and Chief Legal Officer at St. Jude Children's Research Hospital and then served as General Counsel and Board Secretary of Sidra Medicine, an academic medical center in Doha, Qatar, affiliated with Cornell University. In those roles, Clint led legal affairs, technology transfer/licensing, ethics and compliance, board management, and an IRB.

Heather Pearson, Associate, Bass, Berry & Sims PLC

Heather Pearson provides healthcare regulatory and transactional counsel as it relates to compliance, operational matters, and mergers and acquisitions.

Before law school, Heather was a public health analyst at RTI International, focusing on program evaluation and health system financing for the Centers for Medicare & Medicaid Services (CMS). During law school, she summered at the Center for Health Law & Policy Innovation at Harvard Law School and in the Office of the Chief Counsel at the Food & Drug Administration (FDA). Before joining the firm, she served as a term law clerk for the Honorable Damon R. Leichty of the United States District Court for the Northern District of Indiana and the Honorable Carol Hooten of the Minnesota Court of Appeals. Heather earned a law degree from the University of Notre Dame Law School and an undergraduate degree in biomedical anthropology from Wellesley College.