

Establishment Registration: General Information

The Food and Drug Administration (FDA) requires registration of establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps). Manufacture means, but is not limited to, any or all steps in the recovery (collection), processing (such as sterility testing), storage, labeling, packaging or distribution of any human cell or tissue, and the screening or testing for evidence of infectious disease in the tissue donor. Registration is a notice to the FDA of the list of products a facility at the named address manufactures and distributes within or to the U.S. It also provides the information FDA uses to contact establishments.

The FDA has the authority to inspect registered facilities. The inspection will cover all products that are listed in the registration. Facilities in the United States must list all HCT/Ps that are manufactured at their facility.

For international facilities, registration only applies to products that are exported to the U.S. Therefore, international facilities should only list the products that may enter the U.S. regardless of any other HCT/Ps manufactured at their facility. For international partners, listing additional products that will not be exported to the U.S. has the potential to increase the likelihood of an FDA inspection.

Recently, FDA clarified the regulation for registration to exclude facilities doing manufacturing on products under an Investigational New Drug (IND) Application. Registration is still required for facilities that manufacture autologous products, or products from first or second-degree related donors.

NMDP network centers located within the U.S. that manufacture HPC, Apheresis products only for NMDP, do not need to register as these products are under an IND. If those centers also manufacture autologous products or products from first or second-degree related donors they must register. These could include donor centers or apheresis centers.

- NMDP network member cord blood banks, whether located within the U.S. or internationally, that distribute cord blood units under NMDP's 10-CBA IND or another IND, are not required to register. Cord blood banks that hold license from FDA, must comply with requirements of their license.

If an establishment relies on services from other organizations, these organizations may also complete establishment registration and listing with the FDA, such as:

- laboratories performing infectious disease testing (U.S. only)
- laboratories performing bacterial and fungal cultures on hematopoietic stem cells (register as processing)

Tissue Establishment Registration must be completed using the electronic on-line tool: CBER On-Line: Establishment Registration and Biological Product Deviation Reporting. Refer to AID-00085, *Establishment Registration Tool: Electronic Completion of eHCTERS* for step-by-step instructions for completing the electronic Establishment Registration. The FDA Tissue Registration Coordinator may be contacted via email with comments or questions. Contact information is at the end of this document.

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Time Requirements for Registration:

- New establishments must register within 5 days of beginning operations or within 5 days of beginning to export HCT/Ps to the U.S.
- Registered establishments must update their registration annually in December, even if there are no changes to an establishment's HCT/P listing (21 CFR 1271.21).
- Registered establishments need to submit changes to their product listing within 6 months of the change (21 CFR 1271.21).
- If the ownership or location of the establishment changes, the establishment must amend registration information within 30 calendar days of the change (21 CFR 1271.26).
- If a registered facility fails to submit annual renewal, it is a violation of the regulations and that facility would be subject to FDA compliance action and possible fines. Also, failure of an international establishment to register could prohibit or delay entry of a product into the U.S.

Manufacturing Activities:

The following activities meet the definition of manufacturing. Definitions for each function may include but are not limited to:

1. **Recover (collection):** collection of cells or tissues from a human donor by apheresis or collection of umbilical cord blood.
2. **Screen:** screening a cell or tissue donor by review of relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease or disease agents (This includes conducting a health history interview, a physical examination, and review of other readily available relevant medical records).
3. **Test:** perform specified infectious disease testing on a donor using FDA approved donor screening test kits at a laboratory certified under CLIA or equivalent requirements as determined by CMS.
4. **Package:** placing product in bag and packaging for shipment.
5. **Process:** any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as sterility testing, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage
6. **Store:** holding the product for future processing and/or distribution.
7. **Label:** applying labels to products, or management of labels or accompanying materials about the product or the contents that are required to be included with the distributed product.
8. **Distribute:** any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet release criteria.

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The chart illustrates the eight establishment functions for registration with the FDA and which facilities *typically* perform these functions in the NMDP Network:

Establishment Functions*								
Establishment	Recover	Screen	Test	Package	Process	Store	Label	Distribute
Apheresis Center	X			X	X	X	X	X
Donor Center		X					X	
Cord Blood Bank	X	X		X	X	X	X	X
Sterility Testing Laboratory					X			
**Laboratory for IDMs			X					

* Establishment functions may vary from center to center depending upon the operation as it relates to NMDP business or non-NMDP business or agreements in place with other entities.

** Laboratories that perform testing for IDMs must complete establishment registration and listing with the FDA as well; however, the center using the laboratory is responsible for ensuring that the laboratory has completed the registration. U.S. laboratories performing IDM eligibility testing per FDA requirements must complete registration; however most international laboratories do not use FDA approved IDM donor testing kits, and therefore seldom register.

Donor Information:

Most products manufactured for NMDP are from allogeneic (unrelated) donors, and since they are collected under an IND, registration is not required. Some products may be from first- or second-degree relatives of the intended recipient. A facility may manufacture products that fall under more than one category, but registration as a Tissue Establishment is only required for product that are autologous or from a first- or second degree relative. Currently, international network partners do not register for manufacturing HPC, Apheresis products from allogeneic donors. International partners that manufacture autologous or product from first or second-degree related donors must register. Contact your case manager or NMDP contact listed at the end of this document for assistance with this process.

U.S. Agent:

A U.S. agent is required for international establishments only. Official communications between the FDA and an international facility makes use of the U.S. Agent.

The U.S. agent provides the FDA with a contact should U.S. Customs have a question about a product that has arrived at a U.S. port of entry. The U.S. agent also serves as the U.S. contact for an international establishment if the FDA chooses to inspect that international center.

At this time, international establishments that provide products for export to the U.S. only through NMDP may identify Kathy Loper as the U.S. Agent. If a facility exports additional product to the U.S. outside of NMDP, someone other than Kathy Loper must be identified as the U.S. Agent. Also, if a facility has named Kathy Loper as their U.S. Agent, a copy of the validated registration form must be sent to NMDP. See NMDP contact staff listed at the end of this document.

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Importer:

An international facility must name an importer of record for the product. This is defined as a company or individual in the U.S. that is the owner, consignee, or recipient at the time of entry of the foreign establishment's HCT/P that is imported. This should be the transplant center that will receive the product. Contact your case manager or NMDP contact listed at the end of this document to assist with registration for importing products that require registration.

References:

FDA Tissue Registration:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/>

FDA: Tissues and Tissue Products:

<http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm>

FDA Tissue Registration Coordinator: tissuereg@fda.hhs.gov, Phone: (301) 827-6176

NMDP Contact: Regulatory Compliance: regulatory@nmdp.org