

## COMPLIANCE PROGRAM GUIDANCE MANUAL

### Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

7341.002

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**Implementation Date:** July 1, 2005

**Completion Date:** September 30, 2009

**Program/Assignment Codes:**

**41002B for Product Codes:** 57K--01 thru 57K—03 Reproductive Tissue

**41002C for Product Codes:** 57M--01 thru 57M—02 Hematopoietic Stem Cells

**41002D for Product Codes: All other HCT/Ps**

57J--01 thru 57J—06 Musculoskeletal Tissue

57L--01 thru 57L—02 Ocular Tissue

57O-- Other Tissue (human skin, pericardium, dura mater, heart valves)

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### FIELD REPORTING REQUIREMENTS

**Domestic Inspections:** Send a copy of each EIR, and the FACTS coversheet with endorsement and classification to CBER, Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS) HFM-650 (send all EIRS electronically, if possible, to [ITF@cber.fda.gov](mailto:ITF@cber.fda.gov)). Unless the EIR is classified as OAI, do not include exhibits at this time unless specifically requested.

**Foreign Inspections:** Send the complete original EIR, including exhibits, to OCBQ/DIS/HFM-650, regardless of classification. Send a copy of the EIR narrative, and the FACTS coversheet with endorsement to your International Operations Group (IOG) trip coordinator at HFC-130.

**Policy Development or Clarification Only:** Send Establishment Inspection Reports (EIRs) that contain issues requiring policy development or clarification to the Center for Biologics Evaluation and Research (CBER) for review. Send the EIR and relevant exhibits (**electronically, if possible**), to [ITF@cber.fda.gov](mailto:ITF@cber.fda.gov), or by mail to the following address.

Division of Inspections & Surveillance, HFM-650  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
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## **PART I – BACKGROUND**

In the early 1990's, the Centers for Disease Control and Prevention (CDC) reported that human immunodeficiency virus (HIV) had been transmitted through transplantation of human tissue. Information was also reported which suggested that potentially unsafe tissue was being imported into the United States for transplantation into humans. Prompted by reports that potentially unsafe bone was being imported, the Commissioner of Food and Drugs ordered an immediate investigation. Information resulting from this investigation identified an immediate need to protect the public health from the transmission of HIV and hepatitis B and C through transplantation of unsuitable tissue. Concerns that disease transmission could occur, coupled with information derived from these investigations, prompted the Food and Drug Administration (FDA, the Agency) to publish an interim rule in December 1993 that specifically required certain communicable disease testing, donor screening, and record-keeping for human tissue intended for transplantation. A final rule was issued in July 1997.

FDA chose to regulate tissues under the legal authority of Section 361 (Sec. 361) of the Public Health Service Act (hereafter, PHS Act) [42 USC 264]. This section authorizes the Surgeon General, with the approval of the Secretary, Department of Health and Human Services, to make and enforce such regulations as judged necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from State to State. Section 361 of the PHS Act focuses on preventing the introduction, transmission, and spread of communicable diseases.

In 1997, the agency announced its plans for human cells, tissues, and cellular and tissue-based products (HCT/Ps) in two documents: “A Proposed Approach to the Regulation of Cellular and Tissue-Based Products” (62 FR 9721, March 4, 1997) and “Reinventing the Regulation of Human Tissue”. FDA requested written comments on its proposed approach and, on March 17, 1997, held a public meeting to solicit information and views from the interested public. Since that time, the Agency has published three final rules and one interim final rule to implement aspects of the proposed approach.

On January 19, 2001, FDA issued regulations to create a new unified system for registering HCT/P establishments and for listing their HCT/P's (registration final rule, 66 FR 5447). The registration rule became effective in two stages. The first effective date, April 4, 2001 was applicable to establishments that were already regulated under 21 CFR Part 1270. The second effective date was originally January 21, 2003, and was applicable to establishments that manufacture HCT/Ps currently regulated as biological products, drugs, or devices, hematopoietic stem cells from peripheral and cord blood, and reproductive cells and tissues. On January 21, 2003, FDA announced that the registration requirements for these establishments would be further delayed until January 21, 2004.

On January 27, 2004, FDA issued an interim final rule to except human dura mater and human heart valve allografts from the scope of that definition until all of the tissue rules became final. On May 25, 2004, FDA promulgated regulations requiring most cell and tissue donors to be tested and screened for relevant communicable diseases (donor-eligibility final rule, 69 FR 29786). On November 18, 2004, FDA issued regulations that require establishments that manufacture HCT/Ps to comply with Current Good Tissue Practices (CGTP), which would include, among other things, proper handling, processing, labeling, and record-keeping procedures. The regulations require each establishment to maintain a quality program to ensure compliance with CGTP. In addition, with the implementation of CGTPs, human dura mater and human heart valve allografts are now included in the scope of HCT/Ps regulated under 21 CFR 1271. On May 25, 2005 FDA published an interim final rule to revise certain regulations regarding the screening and testing of HCT/P donors and related labeling (interim final rule, 70 FR29949). FDA took this action in response to comments from interested persons regarding the impracticability of complying with certain regulations as they affect particular HCT/Ps.

The CGTP and other regulations are contained in 21 CFR Part 1271, along with provisions relating to establishment registration. These regulations will apply to HCT/Ps recovered on or after the rule's effective date, May 25, 2005. HCT/Ps that were recovered before the effective date of the new rules are subject to 21 CFR 1270, and subparts A and B of Part 1271, as appropriate. In addition, 21 CFR Part 1271 subparts A, B, C, F, 21 CFR 1271.150(c), and 21 CFR 1271.155 of subpart D apply to reproductive HCT/Ps.

The new Part 1271 is made up of six subparts:

- A. - General provisions pertaining to the scope and purpose of Part 1271, as well as definitions.
- B. - Registration and listing procedures.
- C. - Provisions for the screening and testing of donors to determine their eligibility.
- D. - Current Good Tissue Practice (CGTP) requirements.
- E. - Certain labeling and reporting requirements.
- F. - Inspection and enforcement provisions.

21 CFR 1271.10(a) sets out the criteria that form the foundation of our tiered, risk-based approach to regulating HCT/Ps. HCT/Ps that meet all of these criteria are subject only to regulation under section 361 of the PHS Act. These HCT/Ps are subject to the regulations in Part 1271, and no pre-market approval is required. HCT/Ps that do not meet all of the criteria in 21 CFR 1271.10(a) are regulated as drugs, devices, and/or biological products. These HCT/Ps are subject to the regulations specific to drugs, biological products, or medical devices, in addition to applicable sections of Part 1271.

## **PART II – IMPLEMENTATION**

This program provides information about compliance and surveillance activities relating to human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the PHS Act. HCT/Ps are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. The establishments covered by this program are subject to inspection by FDA to determine compliance with the applicable provisions of Title 21, Code of Federal Regulations, Part 1271 (21 CFR Part 1271).

This compliance program covers HCT/Ps recovered on or after May 25, 2005, which are subject to 21 CFR Part 1271 as follows:

- Subparts A through C apply to all HCT/Ps
- Subpart D applies to those HCT/Ps described in 21 CFR 1271.10(a) and regulated solely under section 361 of the PHS Act (most of this subpart is not applicable to reproductive HCT/Ps. See below).
- Subpart E applies only to those HCT/Ps described in 21 CFR 1271.10(a) and regulated solely under section 361 of the PHS Act (this subpart is not applicable to reproductive HCT/Ps).
- 21 CFR Part 1271 subparts A, B, C, F, 21 CFR 1271.150(c), and 21 CFR 1271.155 of subpart D are specifically applicable to reproductive HCT/Ps.

### **A. OBJECTIVE**

This compliance program represents a continuing compliance and surveillance activity conducted to assess whether all HCT/Ps intended for implantation, transplantation, infusion, or transfer are manufactured in accordance with the applicable provisions of 21 CFR Part 1271, to prevent the introduction, transmission, and spread of communicable disease.

This is accomplished by:

1. Providing procedures to investigators conducting inspections of HCT/P establishments;
2. Identifying establishments that are not operating in compliance with the applicable regulations and encouraging voluntary compliance;
3. Providing regulatory and administrative information to compliance officers;
4. Establishing an inventory of establishments active in the HCT/P industry;
5. Taking appropriate enforcement measures.

### **B. PROGRAM MANAGEMENT INSTRUCTIONS**

#### **1. HCT/Ps covered by this program include:**

- Bone (including demineralized bone)
- Ligaments
- Tendons
- Fascia
- Cartilage
- Ocular Tissue (Corneas and Sclera)
- Skin

- Arteries and Veins (except umbilical cord veins)
- Pericardium
- Amniotic membrane (when used alone, without added cells for ocular repair)
- Dura mater
- Heart valve allografts
- Hematopoietic stem/progenitor cells derived from peripheral and cord blood
- Semen
- Oocytes
- Embryos

## 2. 361 HCT/Ps – Definition

The above HCT/Ps are regulated solely under section 361 of the PHS Act and the regulations in 21 CFR Part 1271 if they meet all of the following criteria:

- a. Minimally manipulated;
- b. Intended for a homologous use only as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- c. 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 HCT/P); **AND**
- d. Either:
  - i. Do not have a systemic effect and are not dependent upon the metabolic activity of living cells for the primary function; **OR**
  - ii. Have a systemic effect or are dependent upon the metabolic activity of the other cells for the primary function, **AND:**
    - a) Are for autologous use;
    - b) Are for allogeneic use in a first or second-degree relative; **OR**
    - c) Are for reproductive use

See attachment A for a discussion and complete list of those HCT/Ps not covered by this Compliance Program or for which only certain provisions apply.

During inspections, multiple products may be encountered and each must be considered as to the proper regulation to apply. If it is unclear how the product is regulated because of the way it is processed or manipulated, the Division of Inspections and Surveillance (HFM-650) should be contacted for clarification or guidance (see CBER contacts in Part VI). Investigators should be prepared to provide details regarding the method of processing and the content of the labeling and promotional materials associated with the product to facilitate the decision-making process.

Attachment A is intended to assist Investigators and Compliance Officers in determining which regulations to apply to which products. **Please note: Only HCT/Ps regulated solely under section 361 of the PHS Act are to be covered under this compliance program.** Those HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria and are regulated as drugs, devices, or biological products are covered under separate compliance programs. **If encountered during inspection, determine when/if these products were last inspected by FDA and the review status of the products (e.g. IND). Include this information in the EIR. If deviations are encountered which may impact the safety of such product, investigators should consult with their supervisor and the appropriate product Center to determine the need for expanding the scope of inspectional coverage.**

### 3. **Products covered by other Compliance Programs:**

- **Blood and Blood Products** are covered under CP 7342.001 “Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors”; and CP 7342.002 “Inspection of Source Plasma Establishments”
- **HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria, and are regulated as Medical Devices** are covered under CP 7382.845 “Inspection of Medical Device Manufacturers”
- **HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria, i.e. Autologous, Allogeneic, or Xenogeneic Cells whose biological characteristics have been altered (propagate, pharmacologically treated, etc.); Ex Vivo and Gene Therapy products are regulated as biological drugs** and are covered under CP 7345.848 “Inspection of Biological Drug Products”
- **HCT/Ps recovered before May 25, 2005 and regulated under 21 CFR 1270 and subparts A and B of Part 1271** are covered under CP 7341.002A “Inspection of Tissue Establishments”

### 4. **Establishment Registration, Listing, and Inspection status:**

- All establishments engaged in manufacture (as defined in 21 CFR 1271.3(e)) of an HCT/P must register with and submit to FDA, a list of each human tissue product manufactured unless excepted by 21 CFR 1271.15.
- New establishments must register and list within 5 days of beginning operations.
- CBER maintains an alphabetic listing of currently registered HCT/P establishments that is accessible on the CBER internet web site at <http://www.fda.gov/cber/tissue/hctregistabl.htm>. Questions pertaining to HCT/P establishment registration or product listing should be directed to the CBER Tissue Registration Monitor, HFM-770 (see CBER contacts in Part VI).

### 5. **Donor Eligibility Determination:**

- HCT/P establishments must screen and test HCT/P donors for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases and communicable disease risks associated with xenotransplantation.
- Procedures for all steps that the HCT/P establishment performs in testing, screening, and determining donor eligibility must be established and maintained. These procedures must be designed to ensure compliance with the requirements of subpart C, 21 CFR Part 1271.
- Donor eligibility determination must be based upon the results of donor screening in accordance with 21 CFR 1271.75 and donor testing in accordance with 21 CFR 1271.80 and 1271.85.
- Certain records must accompany the HCT/P at all times once a donor eligibility determination has been made (21 CFR 1271.55). These include a summary of records used to make the donor eligibility determination.
- Until completion of the donor eligibility determination, an HCT/P must be kept in quarantine, and clearly identified as quarantined to prevent improper release and distribution (21 CFR 1271.60).

## **6. Current Good Tissue Practices (CGTPs)**

HCT/P establishments must follow CGTP requirements to prevent the introduction, transmission, or spread of communicable diseases by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing.

The following are Core CGTP requirements as referenced in 21 CFR 1271.150(b):

- a. Requirements relating to facilities (21 CFR 1271.190(a) and (b))
- b. Requirements relating to environmental controls (21 CFR 1271.195(a))
- c. Requirements relating to equipment (21 CFR 1271.200(a))
- d. Requirements relating to supplies and reagents (21 CFR 1271.210(a) and (b))
- e. Requirements relating to recovery (21 CFR 1271.215)
- f. Requirements relating to processing and process controls (21 CFR 1271.220)
- g. Requirements relating to labeling controls (21 CFR 1271.250(a) and (b))
- h. Requirements relating to storage (21 CFR 1271.260(a) – (d))
- i. Requirements relating to receipt, pre-distribution shipment, and distribution of an HCT/P (21 CFR 1271.265(a) – (d)).
- j. Requirements relating to donor eligibility determinations, donor screening, and donor testing (sections 1271.50, 1271.75, 1271.80 and 1271.85).

## **7. Frequency of Inspection:**

There is currently no statutory requirement for FDA to conduct routine biennial inspections of manufacturers of HCT/Ps. Each district should decide which firm(s) to inspect based on the resources they have been allotted in the ORA workplan, and the risk-based selection priorities listed below:

- a. Firms whose last inspection was classified OAI;
- b. Firms for which FDA has received information indicating there is a potential violation of 21 CFR Part 1271.

## **8. Biosafety Precautions for FDA Investigators:**

IOM Section 510 addresses precautions FDA employees should adopt for their own protection. Investigators should be cautious and take suitable precautions to prevent infection in HCT/P establishments or other places where they may be subject to contact with infectious substances. HCT/Ps should be considered potentially infectious and capable of transmitting disease, including HIV and hepatitis.

## **9. FDA Forms used during Inspection:**

At the beginning of each inspection, a Form FDA-482, Notice of Inspection, should be issued to the most responsible individual available at the HCT/P establishment.



**Note:** The Notice of Inspection is not being given pursuant to section 704 of the Food, Drug, and Cosmetic Act, as is the usual case – because HCT/Ps regulated solely under section 361 of the PHS Act are not covered under the Act. Also, issuance of a written notice is not required by section 361 of the PHS Act. However, the agency has decided that it is reasonable and customary to issue an FDA-482 prior to initiating an FDA inspection of a HCT/P establishment. The FDA-482 references Section 361, Part G, of the PHS Act.

At the close of the inspection, observations focusing on the requirements of 21 CFR Part 1271, should be listed on a Form FDA-483 and issued to the most responsible individual.

**10. Assignment of Investigations and Compliance Personnel:**

Where possible, only investigators who completed the Human Tissue Establishment Inspection training (B1216) course should inspect establishments under this compliance program. Where possible, only compliance personnel who have completed this course should process recommendations for compliance actions under this program.

## **PART III – INSPECTIONAL**

### **A. STRATEGY**

The regulations for human cells, tissues, and cellular, and tissue-based products (HCT/Ps) were promulgated under Section 361 of the PHS Act, therefore, inspections of HCT/P establishments must focus on the prevention or introduction, transmission, and spread of communicable disease. If the investigator encounters what are believed to be serious violations during the inspection, the District should alert the CBER/OCBQ/Division of Case Management.

- 1.** Inspection of HCT/P establishments should be conducted according to the requirements in the current good tissue practice (CGTP) regulations. The CGTPs are made up of ten core requirements [21 CFR 1271.150(b)]:
  - a.** Donor requirements relating to:
    - i. Donor eligibility determinations, 21 CFR 1271.50
    - ii. Donor screening, 21 CFR 1271.75
    - iii. Donor testing in 21 CFR 1271.80, and 1271.85
  - b.** Facilities requirements in 21 CFR 1271.190(a) and (b)
  - c.** Environmental Controls requirements in 21 CFR 1271.195(a)
  - d.** Equipment requirements in 21 CFR 1271.200(a)
  - e.** Supplies and Reagents requirements in 21 CFR 1271.210(a) and (b)
  - f.** Recovery requirements in 21 CFR 1271.215
  - g.** Processing and Process Controls requirements in 21 CFR 1271.220
  - h.** Labeling controls requirements in 21 CFR 1271.250(a) and (b)
  - i.** Storage requirements in 21 CFR 1271.260 (a) through (d)
  - j.** Receipt, predistribution shipment, and distribution requirements of an HCT/P in 21 CFR 1271.265 (a) through (d).
- 2.** In order to gain a full understanding of the operations of the HCT/P establishment:
  - a.** See attachments B and C for inspectional information on donor requirements.
  - b.** Determine if the facility is suitable for the functions performed by the establishment, e.g., recovery, screening, testing, processing, storage, labeling, packaging, and distribution, to prevent contamination of the HCT/Ps. The facility should be in a good state of repair, and manufacturing areas must be maintained in a clean sanitary, and orderly manner.
  - c.** Determine if the proper environmental controls and monitoring are in place to prevent contamination or cross contamination of HCT/Ps or equipment. Firms must provide for the following activities/systems where appropriate:
    1. Temperature and humidity controls;
    2. Ventilation and air filtration;
    3. Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations;
    4. Maintenance of equipment used to control conditions necessary for aseptic processing operations.
  - d.** Determine whether equipment is appropriately designed, located, installed, maintained, and cleaned to prevent the introduction, transmission, or spread of communicable diseases. Equipment in use must be capable of producing valid results.

- e. Determine if all supplies and reagents have been verified to meet specifications designed to prevent conditions that increase the risk of introduction, transmission, or spread of communicable disease. Reagents used in the processing /preserving of HCT/Ps must be sterile, where appropriate.
- f. For firms involved in recovery of HCT/Ps, determine if each HCT/P is recovered in a way that does not cause contamination or cross contamination of the product.
- g. Determine if the firm has established appropriate processing and process controls to prevent the introduction, transmission, or spread of disease and contamination or cross-contamination of the product. Pooling of human cells or tissue from 2 or more donors (placed in physical contact or mixed in a single receptacle) is not allowed. Sampling of in-process HCT/Ps must be representative of the material to be evaluated and must meet the process controls established. In the case of dura mater, requirements for process controls are given in 21 CFR 1271.220(d). When the results of processing cannot be fully verified by subsequent inspection and tests, the firm must validate and approve the process according to established procedures. See 21CFR 1271.230 for process validation requirements and attachment D for inspectional guidance.
- h. Determine if the firm has established and maintained procedures to control the labeling of their HCT/Ps. See attachment E for further inspectional guidance.
- i. Determine if the firm is properly controlling storage areas and stock rooms.
  1. Do they prevent the mix-up, contamination, cross contamination of HCT/Ps, supplies, and reagents?
  2. Do they have an adequate area for HCT/Ps that are under quarantine?
  3. Are the HCT/Ps stored at the proper temperature?
  4. Have expiration dates been assigned, where appropriate, in accordance with 1271.260(c)?
  5. Are corrective actions taken and documented whenever proper storage conditions are not met?
- j. Determine how the firm:
  1. Receives incoming HCT/Ps and how they are evaluated.
  2. Makes predistribution shipments of HCT/Ps within their own firm or to outside establishments (contractors).
  3. Documents that HCT/Ps have met release criteria and are available for distribution.
  4. Properly packages and ships HCT/Ps to prevent contamination.
- k. Determine if the establishment has received imported HCT/Ps or if they have received solicitations to purchase foreign HCT/Ps. Inspectional guidance can be found in attachment F.
- l. When a firm performs any manufacturing step, determine if the appropriate tracking procedures are in place, in accordance with 21 CFR 1271.290, to facilitate an investigation of an actual or suspected communicable disease transmission.
- m. Review the manufacturer's complaint file as related to the core CGTPs and ensure they are meeting the requirements set forth in 21 CFR 1271.320.
- n. Contractors that engage in only some operations subject to the CGTP regulations must comply with the regulations covering the operations they perform. See attachment G for inspectional guidance in this area.
- o. NOTE: Not all of the CGTP regulations are being implemented for reproductive HCT/Ps described in 21 CFR 1271.10(a) and regulated solely under section 361 of the PHS Act. See attachment H for inspectional guidance in handling firms that manufacture reproductive HCT/Ps.
- p. NOTE: Certain hematopoietic stem/progenitor cells (HPCs) meet the criteria described in 21 CFR 1271.10(a) and are regulated solely under section 361 of the PHS Act. See attachment I for inspectional guidance on inspections of firms that manufacture HPCs.

## **B. QUALITY PROGRAM (as it relates to core CGTPs)**

Establishments that perform any step in the manufacture of HCT/Ps must establish and maintain a quality program [21 CFR 1271.160] that addresses the core requirements listed in 1271.150(b). The quality program is intended to prevent the introduction, transmission or spread of communicable disease through manufacture and use of HCT/Ps. The program must be appropriate for the specific HCT/P manufactured and the manufacturing steps performed. Functions of the program should include the following:

1. Establishment and maintenance of SOPs that meet the requirements outlined in 21 CFR 1271.180. The procedures should be designed to prevent circumstances that would increase the risk of introduction, transmission, or spread of communicable diseases through the use of the HCT/P. The SOPs must be reviewed and approved, and readily available to the personnel that need them. Any procedures adopted from another organization must be verified to meet the requirements of the CGTPs and appropriate for the step(s) they are intended to cover [21 CFR 1271.160(b)(1)].
2. Procedures must exist for receiving, investigating, evaluating, and documenting information relating to the core CGTP requirements. This would include complaints and sharing any information pertaining to the contamination of the HCT/P [21 CFR 1271.160(b)(2)]
3. Establishments must ensure that corrective actions related to core CGTP requirements are taken and documented. Effectiveness of a corrective action must be verified and, where appropriate, must include both short-term actions taken to address an immediate problem and long-term actions to prevent recurrence. Requirements for the documentation of corrective actions are outlined in 21CFR 1271.160(b)(3).
4. A program should exist that ensures all personnel involved in activities that relate to the core CGTPs requirements are properly trained and educated to perform their job [21 CFR 1271.160(b)(4)].
5. Environmental control [21 CFR 1271.195(a)] is a core GTP requirement. Where appropriate, environmental monitoring systems must be established and appropriately maintained to comply with the CGTPs. [21 CFR 1271.160(b)(5)].
6. HCT/P deviations, as defined in 21 CFR 1271.3(dd)] and trends of HCT/P deviations are required to be investigated and documented. Where appropriate, reporting of deviations relating to core CGTPs for distributed HCT/Ps is required under 21 CFR 1271.350(b). Investigations should include a review and evaluation of the deviation, any efforts to determine the cause, and any corrective action(s) taken [21 CFR 1271.160(b)(6)].

The firm must periodically perform a quality audit, as defined in 21 CFR 1271.3(gg), for management review [21 CFR 1271.160(c)].

**Computers:** The performance of computer software must be validated (if customized) or verified (if used “off-the-shelf”) for the intended use if the firm relies upon it to comply with core CGTP requirements. Requirements are outlined in 21 CFR 1271.160(d). If the firm is using a computerized record-keeping/ tracking system, ensure the integrity of records is maintained and traceability of all HCT/Ps from donor to the consignee or final disposition; and from the consignee or final disposition to the donor.

## **C. PROCEDURES AND RECORDS (as they relate to core CGTPs)**

1. Firms must establish and maintain procedures appropriate to meet the core CGTP requirements in part III (A), for all steps performed in the manufacture of their HCT/Ps. The procedures must

be reviewed and approved by a responsible individual and available to the personnel performing the work. [21 CFR 1271.180]

2. The HCT/P establishment must maintain records concurrently with the performance of each required step in determining donor eligibility and following CGTPs for each HCT/P so that all steps can be clearly traced. All records shall be legible and indelible and shall identify the person performing the work, including dates of the various entries; and shall be as detailed as necessary to provide a complete history of the work performed [21 CFR 1271.270]. Each donor must have a separate and complete record of test results as well as interpretation of the result that is cross-referenced to the HCT/P collected from the donor [21 CFR 1271.55].
3. See attachments J and K for inspectional guidance on record retention and summary of records.

#### **D. REGISTRATION**

Establishments that engage in the manufacture of HCT/Ps currently regulated under section 351 and/or section 361 of the PHS Act, FD&C Act, and 21 CFR 1271 are required to register with FDA and list their HCT/Ps as required in 21 CFR 1271.10(b) and 1271.20. New establishments are required to register and list their HCT/Ps within 5 days after beginning operations defined in 1271.21(a). This includes establishments manufacturing HCT/Ps that meet the definitions in 1271.3(d).

#### **Establishments exempt from registration and product listing at this time**

HCT/P establishments that meet any exception under 1271.15 are exempt from the registration and listing requirements at this time. (See attachment A, part B; listing of establishments exempt from the registration and product listing requirements)

#### **E. REPORTING REQUIREMENTS [21 CFR 1271.350]**

1. All Adverse Reactions (i.e. a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response) that involve a communicable disease related to an HCT/P that was made available for distribution (“available for distribution” means an HCT/P that has been determined to meet all release criteria (1271.3(z).) must be investigated. Adverse Reactions that involve a communicable disease related to an HCT/P must be reported to FDA if it:
  - a. Is fatal;
  - b. Is life-threatening;
  - c. Results in permanent impairment of a body function or permanent damage to body structure; or
  - d. Necessitates medical or surgical intervention, including hospitalization.

The firm must report adverse reactions to CBER (HFM-210) [Form FDA-3500A MedWatch] as soon as possible and no later than 15 calendar days of the initial receipt of the information.

2. All HCT/P deviations (i.e. events that represent a deviation from applicable regulations or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or unexpected or unforeseeable events that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.) related to a distributed HCT/P for which a manufacturing step was performed must be investigated by the firm.

An HCT/P deviation that meets all of the following criteria must be reported to FDA:

- a. related to a distributed HCT/P

- b. related to core GTP
- c. related to the prevention of communicable disease transmission or HCT/P contamination.

The firm must report HCT/P deviations to CBER (HFM-600) [Form FDA 3486] as soon as possible and no later than 45 days of the discovery of the event. Information to be included in the report is as described in 21 CFR 1271.350(b)(2).

ORA investigators have direct access to HCT/P deviation information through CEARS (CBER Error and Accident Reporting System). Instructions for accessing the system are posted on the CEARS Intranet web page. Refer questions to the Email address: [mailto: HCTP\\_deviations@cber.fda.gov](mailto:HCTP_deviations@cber.fda.gov)

To facilitate industry reporting of HCT/P deviations, CBER developed a standardized reporting format (FDA Form 3486) with both hard copy and electronic reporting. CBER encourages electronic reporting.

Website: <http://www.fda.gov/cber/biodev/biodev.htm>

Email address: [HCTP\\_deviations@cber.fda.gov](mailto:HCTP_deviations@cber.fda.gov)

Prior to conducting an inspection, investigators should review the establishment's HCT/P deviation reports in CEARS. Deviation codes may indicate areas the investigator may want to examine more closely for patterns or trends. Otherwise, select a representative sample of reports to verify the adequacy of the firm's corrective action.

## **F. INSPECTION REPORTS**

Report on all areas covered during the inspection, whether in compliance or not (e.g., Does the firm have a quality program in place, and is the firm periodically performing quality audits?).

## **G. INSPECTION PROCEDURES:**

Attachment A.....	Regulatory Considerations
Attachment B .....	Donor Screening
Attachment C.....	Donor Testing
Attachment D.....	Processing and Process Controls
Attachment E.....	Labeling
Attachment F.....	Imports
Attachment G.....	Contractors
Attachment H.....	Reproductive Tissue
Attachment I.....	Hematopoietic stem/Progenitor Cells
Attachment J.....	Records
Attachment K.....	Summary of Records

## **PART IV – ANALYTICAL**

### **NO FIELD ANALYSES ARE PLANNED UNDER THIS PROGRAM.**

The routine collection and analysis of physical samples is not envisioned under this program. If CBER requests sample collection, specific instructions will be provided. Consult with CBER program contacts identified in Part VI, **before** collecting samples for agency analysis, except for documentary samples for interstate commerce (collect a documentary sample in accordance with IOM 405.02 to support regulatory/administrative action).

Contact the CBER Sample Custodian (**301-594-6517**) before shipping any samples to CBER. No one is available to receive samples over the weekend. All samples collected under this program will be shipped to:

Center for Biologics Evaluation and Research  
Attention: Sample Custodian, HFM-235  
5516 Nicholson Lane, Building B, Room 113  
Kensington, MD 20895

Collect any samples of a potentially bio-hazardous nature in accordance with IOM 145.

Original results of analyses will be forwarded to the home district of the involved facility, with a copy to CBER/OCBQ/DCM, HFM-610. Investigators should designate on the FDA-464, Collection Report, to whom the sample results should be forwarded.

Copies of collection reports for physical samples must be submitted to CBER/OCBQ/DCM, HFM-610.

## **PART V – REGULATORY/ADMINISTRATIVE STRATEGY**

This part provides the regulatory/administrative strategy pertaining to enforcement for all human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are regulated solely under the authority of section 361 of the PHS Act and are in violation of the provisions of 21 CFR 1271. HCT/Ps recovered by foreign manufacturers are subject to the same advisory, administrative, and judicial actions as HCT/Ps recovered domestically.

Significant objectionable conditions should be brought to the firm's attention on an FDA Form-483, Inspectional Observations, at the conclusion of the inspection (See IOM 512). The evaluation of inspectional findings and any resultant recommendation for regulatory action will be conducted in accordance with existing procedures and the RPM. The strategy and actions outlined below are those believed to be most appropriate and expeditious when significant deficiencies are observed and documented.

The decision on the type of action to recommend should be based on the seriousness of the documented deficiencies, and the most effective way to protect the public health.

A firm's written corrective actions, in response to the FDA Form-483, should not preclude the consideration of an advisory, administrative, or judicial action. If the objectionable observations represent a continuing pattern of non-compliance, a failure to correct significant deficiencies noted during a previous inspection, or the deficiencies pose a serious threat to the public health, and voluntary action is either not appropriate or can not be readily accomplished, the appropriate advisory, administrative, or judicial action should be recommended.

The investigator should verify through actual observation, whenever possible, whether or not the firm adheres to the applicable regulations and the law. Well-documented donor eligibility and/or CGTP deficiencies provide the evidence for concluding that a firm is not operating in compliance with section 361 of the PHS Act and the applicable regulations. Evidence of serious deficiencies within areas of the firm's operations that relate directly to introduction, transmission or spread of communicable disease generally indicates that significant problems exist. When the inspectional findings demonstrate that a firm is operating in significant non-compliance, and/or the establishment's management is either unwilling or unable to implement full corrections in a timely manner, administrative or judicial action should be considered.

To consider taking any type of regulatory action, serious deficiencies should be well documented with supporting evidence. The quality of any action begins with the quality of evidence collected at the time of the inspection, to support the observed objectionable conditions. The recognition, collection, and effective presentation of evidence are essential to any successful advisory, administrative, or judicial action. Establish individual responsibility, and identify persons to hold accountable for violations and with whom the agency should communicate to seek lasting corrections, and/or to be the subject of enforcement actions.

Submit recommendations for regulatory action to the Center for Biologics Evaluation and Research (CBER)/Office of Compliance and Biologics Quality (OCBQ)/Division of Case Management (DCM)/HFM-610.



For HCT/Ps regulated solely under Section 361 of the PHS Act and 21 CFR 1271, the advisory, administrative, and judicial options available include:

Action	Among other things, consider if,
Untitled Letter	Violations that do not meet the threshold of regulatory significance for a Warning Letter; however, regulatory concerns exist that cannot be addressed through other means (e.g., 483 response review letter).
Warning Letter	Violations of regulatory significance suggesting that systemic problems exist within one or more areas of the firm's operations.
Order of Retention, Recall, Destruction (21 CFR 1271.440 (a)(1 & 2))	<p>Significant deviations suggesting that there are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations, and therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or an establishment is in violation of the regulations, such that the conditions of manufacture of the HCT/P do not provide adequate protections against the risks of communicable disease transmission</p> <p><b>NOTE:</b> Upon findings of violative HCT/Ps that may warrant issuance of an Order of Retention, Recall, Destruction, investigators should contact the supervisor/team leader and the responsible district management. If there is confirmation of significant deficiencies, notify CBER/DCM as early as possible to ensure collection of all necessary documentation.</p>
Order of Cessation of Manufacturing (21 CFR 1271.440(a)(3))	<p>Significant deviations suggesting there are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations, and therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or an establishment is in violation of the regulations, such that the conditions of manufacture of the HCT/P do not provide adequate protections against the risks of communicable disease transmission and therefore, there are reasonable grounds to believe that a danger to health exists.</p> <p><b>NOTE:</b> Upon findings of significant deficiencies that may warrant issuance of an Order of Cessation of Manufacturing, investigators should contact the supervisor/team leader and the responsible district management. If there is confirmation of significant deficiencies, notify CBER/DCM as early as possible to ensure collection of all necessary documentation.</p>
Prosecution	Gross, flagrant or intentional violations, fraud, danger to health, or continued or repeated course of violative conduct.

Before judicial intervention is attempted, the district should first consider issuance of an Untitled Letter, Warning Letter or, if appropriate, the administrative remedies of orders of retention, recall, destruction, and/or cessation of manufacturing outlined in the regulation, 21 CFR 1271.440. FDA may order that the HCT/P be recalled and destroyed, and that persons in possession of the HCT/P retain it until it is recalled by the distributor, destroyed, or disposed of as agreed to by FDA, or the safety of the HCT/P is confirmed. FDA is also authorized to take possession of and/or destroy the violative HCT/P; however, this should only be done as a last resort. Additionally, FDA may order an establishment to cease one or

more steps in the manufacture of an HCT/P until compliance with the applicable regulations has been achieved.

**NOTE:** There is no direct reference authority for the issuance of Untitled Letters, Warning Letters or orders of retention, recall, destruction, and cessation of manufacturing.

**NOTE:** Depending on the circumstances, there may be situations where both a Warning Letter and an order of retention, recall, and/or destruction are warranted.

## **A. WARNING LETTER**

A Warning Letter (WL) may be issued to an establishment when FDA considers one or more of its products and/or practices to be in violation of 21 CFR 1271. The issuance of a WL may be appropriate in cases when findings suggest that systemic problems in area(s) of a firm's operations or procedures need to be brought into compliance with 21 CFR 1271. The violations cited should be appropriate for the issuance of a WL (e.g. significant deficiencies, recurring or continuing deficiencies). There should be reasonable expectation that correction will be prompt, and there must be sufficient documentation of the violations. In addition, the WL can include notification to the firm of the need to bring violative HCT/Ps into compliance (e.g., product quarantine or notification to consignees), if necessary. A WL also establishes prior notice if further action becomes necessary.

The WL recommendation along with a draft WL should be forwarded to the Division of Case Management (HFM-610) within 15 working days of the inspection. If the Division of Case Management and the Office of General Counsel (OGC) concur with the recommendation, the district should issue the WL as soon as possible.

Refer to RPM Chapter 4, Subchapter "Warning Letters," for procedural instructions for issuance of a Warning Letter.

## **B. ORDER OF RETENTION, RECALL AND/OR DESTRUCTION**

The option to order retention, recall and/or destruction of violative HCT/Ps is available to FDA under 21 CFR 1271.440(a)(1 & 2) and is used when the Agency determines that it must act to prevent the distribution of a violative HCT/P that may result in the introduction, transmission, or spread of communicable diseases. This may be as a result of findings that there are reasonable grounds to believe an HCT/P is a violative HCT/P because it was manufactured in violation of subparts C or D of the regulations, and therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission, or an HCT/P is infected or contaminated so as to be a source of dangerous infection to humans.

The deviations must be well documented. Situations where there are significant concerns regarding the source or violation of the HCT/P, the adequacy of the screening and/or testing, or a failure of the establishment to fulfill stated commitments to gain control over violative HCT/Ps may result in the issuance of an order of retention, recall and/or destruction.

The regulations permit FDA and the HCT/P establishment to develop a strategy regarding the disposal of violative HCT/Ps. Within the provisions of the order of retention, recall and/or destruction, the establishment is permitted to implement corrective action to bring the violative HCT/P into compliance. If the violative HCT/Ps can be reconditioned to become suitable for implantation, transplantation, infusion, or transfer into a human recipient as a result of these corrective actions, the district may authorize release of the HCT/P for distribution. Unless an alternate resolution can be found, the violative

HCT/P must be recalled and/or destroyed within 5 working days of receipt of the order of retention, recall and/or destruction.

The regulations, according to 21 CFR 1271.440(e), also permit establishments/individuals to request a Part 16 hearing regarding FDA's orders of retention, recall and/or destruction within 5 working days of receipt of the order of retention, recall and/or destruction. If a hearing is requested, destruction of the violative HCT/P is placed in abeyance. However, the provisions of the order of retention, recall and /or destruction regarding recall and retention of violative HCT/P remain in place and are not impacted by the hearing request.

**NOTE:** FDA will not issue an order for the destruction of reproductive tissue under paragraph 21 CFR 1271.440 (a)(1), nor will it carry out such destruction itself under paragraph 21 CFR 1271.440 (a)(2).

Refer to RPM Chapter 5, Subchapter "Orders of Retention, Recall, Destruction and Cessation of Manufacturing Related to Human Cells, Tissue, and Cellular and Tissue-Based Products (HCT/Ps)," for procedural instructions for issuance of an order.

### **C. ORDER OF CESSATION OF MANUFACTURING**

Pursuant to 21 CFR 1271.440(a)(3), the Agency may order an establishment to cease one or more steps in the manufacture of an HCT/P upon finding that there are reasonable grounds to believe the HCT/P is a violative HCT/P because:

- Establishment is in violation of the regulations, such that adequate protections are not provided against the risks of communicable disease transmission and therefore, a danger to health exists; or
- HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or
- HCT/P was manufactured in violation of the regulations and, therefore, the condition of manufacture of the HCT/P does not provide adequate protections against risks of communicable disease transmission.

As with an order of retention, recall and/or destruction in considering an order of cessation of manufacturing, the deviations must be well documented. Situations where a danger to health exists may result in the immediate issuance of an order of cessation of manufacturing. Situations where there are significant concerns regarding one or more steps in the manufacture of HCT/Ps, or a failure of the establishment to fulfill stated commitments to gain control over or to bring the areas of manufacturing into compliance with the applicable regulations may result in the issuance of an order of cessation of manufacturing although the effective date may be delayed in certain circumstances.

Within the provisions of the order of cessation of manufacturing, the establishment is permitted to implement corrective action to bring its operations into compliance. However, the firm may not resume operations without receipt of written authorization from FDA.

The regulations, according to 21 CFR 1271.440(e), also permit establishments/individuals to request a Part 16 hearing regarding FDA's order of cessation of manufacturing within 5 working days of receipt of the order of cessation of manufacturing. An expedited hearing will be afforded for an order of cessation that is not stayed by the Commissioner of Food and Drugs.

Refer to RPM Chapter 5, Subchapter "Orders of Retention, Recall, Destruction and Cessation of Manufacturing Related to Human Cells, Tissue, and Cellular and Tissue-Based Products (HCT/Ps)," for procedural instructions for issuance of an order.

**NOTE:** Timeliness is very important in the decision to issue an order of retention, recall, destruction, and/or cessation of manufacturing; otherwise the perceived seriousness of a firm's non-compliance may be diminished. Contact DCM as early as possible if findings suggest that an order of retention, recall, destruction, and/or cessation of manufacturing may be warranted. Recommendations for issuance of orders of cessation of manufacturing are given high priority and districts are to act promptly.

## **D. PROSECUTION**

It is Agency policy to consider prosecution of individuals when there is documented evidence of fraud, gross violations, a hazard to health and/or continuing significant violations. With the exception of prosecutions involving gross, flagrant, or intentional violations, fraud, or danger to health, the criminal charges should show a continuous or repeated course of violative conduct. This may consist of counts from two or more inspections, or counts from separate violative shipments at different points in time.

Sections 3559 and 3571(c) of Title 18, United States Code (18 USC), and section 368 of the PHS Act are the applicable statutes when pursuing prosecution for violating regulations promulgated under Section 361 of the PHS Act. Under section 368(a) of the PHS Act, any individual who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Additionally, individuals may be punished by a fine of up to \$100,000 if death has not resulted from a violation of the regulations or up to \$250,000 if death has resulted.

Specific guidance and models for prosecutions have not yet been established, and districts should refer to RPM Chapter 6, Subchapter "Prosecutions," for general procedural instructions concerning prosecution.

## **E. DEFICIENCIES**

Examples of donor eligibility deficiencies and deficiencies related to the CGTPs:

### **1. Donor Eligibility**

- Any failure in the determination of the eligibility of donors that causes the establishment to accept ineligible donors [21 CFR 1271.50(a), 1271.75, 1271.80, 1271.85]
- Failure to have records accompanying an HCT/P at all times after the donor-eligibility determination is complete [21 CFR 1271.55(a)]
- Any failure resulting in the HCT/P being released from quarantine prior to the completion of donor-eligibility determination [21 CFR 1271.60(a)]
- Failure to store or identify HCT/Ps from a donor determined to be ineligible in a clearly identified physically separate area or to follow other procedures, such as automated designations, that are adequate to prevent improper release [21 CFR 1271.65(a)]

### **2. CGTPs**

- Any issue in size, construction, location, cleanliness or sanitation that causes a facility to allow the introduction, transmission, or spread of communicable disease agents [21 CFR 1271.190(a) & (b)]
- Failure to adequately control environmental conditions and to provide for proper conditions for operations [21 CFR 1271.195(a)]

- Any failure in equipment and/or procedures for cleaning, sanitizing, and maintenance of equipment resulting in introduction, transmission, or spread of communicable disease agents [21 CFR 1271.200(a) & (b)]
- Failure to assure that supplies and reagents used in the manufacturing of an HCT/P do not introduce, transmit, or spread communicable disease agents [21 CFR 1271.210(a) & (b)]
- Any failure in the recovery of HCT/Ps that causes the introduction, transmission, or spread of communicable disease agents [21 CFR 1271.215]
- Any failure in processing or in-process control and testing resulting in the contamination or cross-contamination and the introduction, transmission, or spread of communicable disease agents of HCT/Ps [21 CFR 1271.200 (a) & (c)]
- Pooling of HCT/Ps from two or more donors during processing [21 CFR 1271.200(b)]
- Failure to establish and maintain procedures to control the labeling of HCT/Ps, including verification of the label's accuracy, legibility, and integrity [21 CFR 1271.250(a) & (b)]
- Any failure in the storage of HCT/Ps, including control of storage areas, temperature, expiration date [21 CFR 1271.260(a) through (c)]
- Failure to document corrective actions resulting from proper storage conditions not being met [21 CFR 1271.260(d)]
- Any failure in the evaluation of incoming tissue for the presence and significance of microorganisms or inspection of incoming tissue for the presence of damage and contamination [21 CFR 1271.265(a)]
- Any failure in the pre-distribution and the availability for distribution of HCT/Ps [21 CFR 1271.265(b) & (c)]
- Design and construction of packaging and shipping containers are inadequate to protect the HCT/P from contamination [21 CFR 1271.265(d)]
- Failure to establish and maintain procedures for the receipt, pre-distribution shipment, and distribution of an HCT/P [21 CFR 1271.265(e)]
- Failure to maintain appropriate records [21 CFR 1271.270]
- Failure to establish and maintain procedures for the review, evaluation, and documentation of complaint files [21 CFR 1271.230(a)]
- Any failure in the verification or validation of a process or a change in a process [21 CFR 1271.225 and 1271.230(a)]
- Failure to establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable disease agents [21 CFR 1271.160(a)]
- Failure to establish and maintain procedures appropriate to meet core CGTPs requirements [21 CFR 1271.180(a)]

## **PART VI – REFERENCES AND PROGRAM CONTACTS**

### **A. REFERENCES**

- Public Health Service (PHS) Act, Sections 361 and 368 [42 U.S.C. 264 and 271]
- Title 21, Code of Federal Regulations (21 CFR), Parts 16, 1271  
[<http://first.fda.gov/fedreg/html/links.htm>]
- March 4, 1997 Proposed Approach To Regulation of Cellular and Tissue-Based Products [62 FR 9721] [[www.fda.gov/cber/gdlns/CELLTISSUE.txt](http://www.fda.gov/cber/gdlns/CELLTISSUE.txt)]
- July 29, 1997 Final Rule: Human Tissue Intended for Transplantation [62 FR 40429]  
[[www.fda.gov/cber/genadmin/frtissue.txt](http://www.fda.gov/cber/genadmin/frtissue.txt)]
- January 19, 2001 Final Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products, Establishment Registration and Listing [66 FR 5447]  
[[www.fda.gov/cber/rules/frtisreg011901.htm](http://www.fda.gov/cber/rules/frtisreg011901.htm)]
- January 21, 2003 Final Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products, Establishment Registration and Listing – Delay of Effective Date [68 FR 2689]  
[[www.fda.gov/cber/rules/frtisreg012103.htm](http://www.fda.gov/cber/rules/frtisreg012103.htm)]
- January 27, 2004 Interim Final Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products, Establishment Registration and Listing [69 FR 3823]  
[[www.fda.gov/cber/rules/frtisreg012304.htm](http://www.fda.gov/cber/rules/frtisreg012304.htm)]
- May 25, 2004 Final Rule: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [69 FR 29785] [[www.fda.gov/cber/rules/suitdonor.htm](http://www.fda.gov/cber/rules/suitdonor.htm)]
- November 24, 2004 Final Rule: Current Good Tissue Practice for Human Cells, Tissues, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement [69 FR 68611]  
[[www.fda.gov/cber/rules/gtp.htm](http://www.fda.gov/cber/rules/gtp.htm)]
- Alphabetical List of Registered Tissue Establishments  
[[www.fda.gov/cber/tissue/hctregistabl.htm](http://www.fda.gov/cber/tissue/hctregistabl.htm)]

### **B. INSPECTION OPERATIONS MANUAL (IOM)**

- Chapter 1 – Administration, Subchapter 140 – Safety, 145 – Microbiological Hazards
- Chapter 5 – Establishment Inspections, Subchapter 560 – Biologics
- Chapter 6 – Imports, Subchapter 630 – Field Examinations, 635 – Biologics
- Chapter 7 – Regulatory, Subchapter 770 – Regulatory Submissions, 773 – Center for Biologics Evaluation and Research (CBER)
- Chapter 9 – Investigation, Subchapter 920 – Injury and Adverse Reactions, 924 – Biologics – Injury, Reaction, or Fatality

### **C. REGULATORY PROCEDURES MANUAL (RPM)**

- Chapter 4 Advisory Actions (Warning Letters and Untitled Letters)
- Chapter 5 Administrative Actions (Order of Retention, Recall, Destruction and Cessation of Manufacture Related to Human Cells, Tissue, Cellular and Tissue-Based Products (HCT/Ps))
- Chapter 6 Judicial Actions
- Chapter 7 Recall Procedures (Mandatory Recalls of Human Cells, Tissue, Cellular and Tissue-Based Products (HCT/Ps))
- Chapter 9, Subchapter - Importation of Biological Products

## D. INDUSTRY STANDARDS

Standards for Tissue Banking, April 2002, American Association of Tissue Banks, 1320 Old Chain Bridge Road, Suite 450, McLean, VA 22101

Eye Bank Association of America Medical Standards, October 2004, Eye Bank Association of America, 1015 18<sup>th</sup> Street, NW, Suite 1010, Washington, DC 20036

AABB Standards for Cellular Therapy Product Services, First Edition, 2004, AABB, 8101 Glenbrook Road, Bethesda, MD 20814-2749

Foundation for the Accreditation of Cellular Therapy (FACT) Standards for Hematopoietic Progenitor Cell Collection, Processing, and Transplantation, Second Edition, 2002, FACT, 986065 Nebraska Medical Center, Omaha, NE 68198-6065

Netcord/FACT International Cord Blood Standards, Second Edition 2002, FACT, 986065 Nebraska Medical Center, Omaha, NE 68198-6065

Circular of Information for the Use of Cellular Therapy products, AABB Press, Bethesda, MD, October 2003

## E. MEMORANDA AND GUIDELINES

“Guidance for Industry: Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (November 2004) [[www.fda.gov/cber/tissue/docs.htm](http://www.fda.gov/cber/tissue/docs.htm)] (PDF)

“Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (May 2004) [[www.fda.gov/cber/gdlns/tissdonor.htm](http://www.fda.gov/cber/gdlns/tissdonor.htm)]

“Draft Guidance for Industry: Sterile Drug Product Produced by Aseptic Processing, Current Good Manufacturing Practice” (August 2003) [<http://www.fda.gov/cber/gdlns/steraseptic.htm>]

“Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (June 2002) <http://www.fda.gov/cber/gdlns/cjdvcjd0602.htm>

“Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P’s)” (May 2002) distinguishes between tissues regulated by CDRH as devices and tissues regulated by CBER. [See ATTACHMENT B]

“Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens” (June 2000) [[www.fda.gov/cber/gdlns/cadbld.htm](http://www.fda.gov/cber/gdlns/cadbld.htm)]

Guide to Inspection of Infectious Disease Marker Testing Facilities (June 1996)

PHS/CDC "Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs" MMWR 1994;43/RR-8; 1-17

PHS "Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C" MMWR 1991;40/RR-4; 1-17

## F. PROGRAM CONTACTS (CBER AND ORA)

### 1. CBER/OCBQ Division of Inspections & Surveillance (DIS), HFM-650

301-827-6220/ fax 301-827-6748

**Program Surveillance Branch, HFM-654**

Janet Ishimoto, Chief

Function:

Tissue safety, surveillance and compliance  
Provide inspectional guidance regarding tissues  
Review of FDA-483s

Hang Dinh, CSO

Bima Patel, CSO

**2. CBER/OCBQ Division of Case Management (DCM), HFM-610**

301-827-6201/ fax 301-5940940

**Blood and Tissue Compliance Branch (BTCB), HFM-614**

Function:

Process recommendations for administrative and legal action  
Orders of retention, recall, destruction, and/or cessation of manufacturing  
Untitled Letters, Warning Letters, Injunctions, Prosecutions

Stephany Wesley, Chief

Contact any CSO in BTCB

**Biological Drug and Device Compliance Branch (BDDCB), HFM-625**

Function:

Provide guidance regarding imports and exports of products that fall under CBER's purview, including HCT/Ps.

Diane Alexander, Chief

**3. CBER/Office of Cells, Tissues and Gene Therapy (OCTGT)**

**Division of Human Tissues, HFM-770**

301-827-0078/ fax 301-827-2844

Function:

Regulatory oversight of the HCT/P industry

Ruth Solomon, MD, Director

Melissa Greenwald, MD

Ellen Lazarus, MD

Martha Wells, M.P.H.

Rosemarie Wiseman, Tissue Registration Monitor 301-827-6176

**4. ORA CONTACT ORA/ORO/DFI/HFC-130**

301-827-5662/ fax 301-443-3757

Gail Katz, CSO

Mary Carden, CSO, National Expert, Blood and Tissue Program



## **PART VII – COORDINATION AND PROGRAM MONITORING**

CBER/OCBQ/DIS will work cooperatively with ORA, and the Biological Products Field Committee, to monitor the inspectional and compliance accomplishments under this compliance program, and the status of the inspected industry establishments.

The ORA annual workplan, developed by CBER and ORA, provides overall resource allocations and anticipated numbers of inspections. However, current industry practices encountered during an inspection, the past compliance history of establishments, or other compliance developments, may necessarily result in unplanned inspections or in individual inspections taking more or less time than estimated in the workplan.

As is customary, ORA continues to have the primary responsibility for ensuring:

- (1) That the program strategies, priorities, and procedures articulated in this compliance program are followed by the ORA staff, and
- (2) Potential problems or needs for policy/program clarification are brought to the attention of CBER/OCBQ.

CBER and ORA jointly coordinate activities to achieve industry compliance with applicable laws, regulations, and orders (e.g., orders of retention, recall, destruction and/or cessation of manufacturing).

CBER/OCBQ will continue to use accomplishment data from the ORA Field Accomplishment and Compliance Tracking System (FACTS), administrative or judicial action recommendations, requests for policy decisions/clarification received from the public or the industry, and input from CBER scientific and product experts to develop inspectional history within the industry.

## **ATTACHMENT A – REGULATORY CONSIDERATIONS**

This attachment is intended as an inspectional tool to assist FDA Investigators and Compliance Officers in distinguishing between the human cells, tissues, and cellular and tissue-based products (HCT/P's), as defined in 21 CFR 1271.3(d), that **DO NOT** meet all of the criteria described in 21 CFR 1271.10(a). These types of HCT/Ps are regulated by the Center for Devices and Radiological Health (CDRH) as medical devices, are regulated by the Center for Drug Evaluation and Research (CDER) as drug products, or are regulated by the Center for Biologics Evaluation and Research (CBER) as biological products. A section is also included for combination products.

**HCT/Ps THAT DO NOT MEET ALL 21 CFR 1271.10(a) CRITERIA ARE NOT COVERED UNDER THIS COMPLIANCE PROGRAM.** If encountered during inspection, determine when/if these products were last inspected by FDA and the review status of the products (e.g. IND). Do not specifically review products that are not covered under this compliance program. Note in the EIR that these products are being “manufactured” at the firm, along with the last inspection date and review status, if applicable. If deviations are found that may have an impact on product safety, consult with your supervisor and the appropriate product Center to determine the need to expand the scope of inspectional coverage.

### **A. HCT/Ps THAT DO NOT MEET ALL 21 CFR 1271.10(a) CRITERIA:**

#### **1. CBER**

Human cell therapy and gene therapy products are regulated under Section 351 of the PHS Act and/or the FD&C Act, biologics/drug regulations, 21 CFR 210, 211, 600 – 680, and HCT/P regulations, 21 CFR 1271 subparts A – D

This grouping includes products that FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products:

- Cultured cartilage cells
- Cultured nerve cells
- Lymphocyte immune therapy [[www.fda.gov/cber/ltr/lit013002.htm](http://www.fda.gov/cber/ltr/lit013002.htm)]
- Gene therapy products
- Human cloning [[www.fda.gov/cber/ltr/aaclone.htm](http://www.fda.gov/cber/ltr/aaclone.htm)]
- Human cells used in therapy involving the transfer of genetic material (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector) [[www.fda.gov/cber/ltr/cytotrans070601.htm](http://www.fda.gov/cber/ltr/cytotrans070601.htm)]
- Unrelated allogeneic hematopoietic stem cells
- Unrelated donor lymphocytes for infusion.

Blood and blood products are regulated under Section 351 of the PHS Act, the FD&C Act, and blood regulations, 21 CFR 600 – 680

## **2. CDRH**

Devices composed of human tissues are regulated under the FD&C Act, device regulations, 21 CFR 820, HCT/P regulations 21 CFR 1271 subparts A – D, and/or Section 351 of the PHS Act. Such devices include:

- Corneal lenticules
- Preserved umbilical cord vein grafts
- Human collagen
- Femoral veins intended as A-V shunts.

## **3. COMBINATION PRODUCTS**

- Demineralized bone combined with handling agents (glycerol, sodium hyaluronate, calcium sulfate, gelatin, collagen) – are regulated as devices
- Bone-suture-tendon allografts – regulated as devices
- Cultured cells (fibroblasts/keratinocytes/ neurons/chondrocytes) on synthetic membranes or combined with collagen are regulated as devices or Biological products
- Encapsulated pancreatic islet cells are regulated as Biological products.

## **4. OTHER PRODUCTS NOT COVERED BY THIS COMPLIANCE PROGRAM**

- Vascularized human organs for transplantation (kidneys, lungs, heart, liver, pancreas, including vascularized subparts of human organs) are regulated by Health Resources and Services Administration (HRSA)
- Minimally manipulated bone marrow are regulated by Health Resources and Services Administration (HRSA)
- Secreted or extract human products such as milk, collagen, and cell factors
- Ancillary products used in the manufacture of an HCT/P
- Cells, tissues, and organs derived from animals other than humans
- In-Vitro Diagnostic products

## **5. PRODUCTS COVERED BY OTHER COMPLIANCE PROGRAMS**

- Blood and Blood products are covered under CP 7342.001, “Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors”; and CP 7342.002, “Inspection of Source Plasma Establishments”
- HCT/Ps regulated as Medical Devices are covered under CP 7382.845, “Inspection of Medical Device Manufacturers”
- HCT/Ps regulated as Biological Products are covered under CP 7345.848, “Inspection of Biological Drug Products”
- Human Tissue collected before May 25, 2005 are covered under CP 7341.002A, “Inspection of Tissue Establishments”

## **B. EXCEPTIONS AND EXEMPTIONS**

21 CFR 1271.10(a) describes those HCT/Ps that are regulated solely under section 361 of the PHS Act. Throughout 21 CFR 1271 there are exceptions and/or exemptions to the regulations. These exceptions and exemptions are noted here. For additional guidance on how to proceed during inspection, refer to attachments B – K:

### **1. SUBPART B -- REGISTRATION 21 CFR 1271.15:**

- a.** If the firm uses HCT/Ps for educational or non-clinical scientific purposes they DO NOT have to register and list products
- b.** If the firm removes HCT/Ps from an individual and re-implants those SAME HCT/Ps into the SAME individual during the SAME surgical procedure, they DO NOT have to register and list products
- c.** If the firm only transports HCT/Ps, they DO NOT have to register and list products
- d.** If the firm only receives and/or stores HCT/Ps for use within the facility, they DO NOT have to register and list products
- e.** If the firm only recovers reproductive HCT/Ps for immediate transfer into the sexually intimate partner of the donor, they DO NOT have to register and list products
- f.** If an individual only recovers HCT/Ps under contract with a registered establishment, and sends recovered HCT/Ps directly to the registered establishment, he/she DOES NOT have to register and list products; HOWEVER, he/she is required to follow those regulations pertaining to the manufacturing step(s) performed, and may be assessed when the registered establishment is inspected.

### **2. SUBPART C -- DONOR ELIGIBILITY 21 CFR 1271.60(d), 1271.65(b), AND 1271.90**

- a.** Urgent medical need 21 CFR 1271.60(d)
  - i.** If an urgent medical need is demonstrated for an HCT/P for which a donor eligibility determination has not been made, the HCT/P may be implanted, transplanted, infused, or transferred, provided it is prominently labeled “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” and “WARNING: Advise patient of communicable disease risks”; in addition, the following records must accompany the HCT/P:
    - 1) The results of any donor screening that has been completed;
    - 2) The results of any donor testing that has been completed;
    - 3) A list of any required donor screening or testing that has not been completed.
  - ii.** The firm must document that the physician was notified that donor screening and/or testing were not completed;
  - iii.** The firm must complete donor screening and/or testing during or after use of the HCT/P and make a donor eligibility determination;
  - iv.** The physician must be informed of the results of the donor eligibility determination.
- b.** Limited uses of HCT/Ps from ineligible donors 21 CFR 1271.65(b)
  - i.** HCT/Ps from an ineligible donor may be implanted, transplanted, infused, or transferred provided:
    - 1) The HCT/P is for allogeneic use in a first or second-degree blood relative;
    - 2) The HCT/P consists of reproductive cells or tissue from a directed donor; or
    - 3) There is a documented urgent medical need.

- ii. The HCT/P must be labeled with the biohazard legend and a statement “WARNING: Advise patient of communicable disease risks”;
- iii. If donor testing results are reactive, the HCT/P must be labeled as noted in #2 and with the statement “WARNING: Reactive test results for (name of disease agent or disease)”;
- iv. The HCT/P must be accompanied by records as required in 21 CFR 1271.55
- v. The firm must document that the physician using the HCT/P was notified of screening and/or test results.

**c. Donor eligibility exceptions 21 CFR 1271.90**

HCT/P establishments DO NOT have to determine donor eligibility for the following:

- i. HCT/Ps for autologous use;
- ii. Reproductive HCT/Ps donated by a sexually intimate partner of the recipient for reproductive use;
- iii. Cryopreserved HCT/Ps for reproductive use subsequently intended for directed donations provided:
  - 1) Additional donations are unavailable;
  - 2) Appropriate measures are taken to screen and test donors before transfer to recipient (as a directed donation, donor is no longer exempt, so screening and testing apply).
- iv. Appropriate labeling for autologous use HCT/Ps: “FOR AUTOLOGOUS USE ONLY”;
- v. If the firm has not performed applicable screening and/or testing: “NOT EVALUATED FOR INFECTIOUS SUBSTANCES”; and “WARNING: Advise patient of communicable disease risks”;
- vi. If screening and/or testing has been performed with reactive results: “WARNING: Advise patient of communicable disease risks” and “WARNING: Reactive test results for (name of the disease agent or disease)” and include biohazard legend.

**3. SUBPART D – CURRENT GOOD TISSUE PRACTICE**

Subpart D is not applicable to reproductive HCT/Ps, except the provisions in 1271.150(c) and 1271.155.

**4. SUBPART E – ADDITIONAL REQUIREMENTS FOR ESTABLISHMENTS DESCRIBED IN 21 CFR 1271.10**

The provisions in subpart E for reporting adverse reactions, HCT/P deviations, and for labeling are:

- a. Not applicable to reproductive HCT/Ps
- b. Not applicable to HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria and are regulated as drugs, devices, or biological products

**5. SUBPART F – INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 21 CFR 1271.10**

The provisions of subpart F are not applicable to HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria. Such products are regulated as drugs, devices, or biological products

FDA will not issue an order for the destruction of reproductive tissue under paragraph 21 CFR 1271.440 (a)(1), nor will it carry out such destruction itself under paragraph 21 CFR 1271.440 (a)(2).

**6. HCT/Ps OFFERED FOR IMPORT 21 CFR 1271.420 (c) and (d)**

Import regulations in 21 CFR 1271.420 are not applicable to:

- a.** reproductive HCT/Ps donated by a sexually intimate partner of the recipient for reproductive use;
- b.** peripheral blood stem/progenitor cells except when circumstances occur under which the cells may present an unreasonable risk of communicable disease transmission, which indicates the need to review information to make an admissibility decision; or
- c.** HCT/Ps that do not meet all 21 CFR 1271.10(a) criteria and are regulated as drugs, devices, or biological products

Refer to attachment F for additional inspection guidance regarding HCT/Ps offered for Import.

## **ATTACHMENT B – DONOR SCREENING**

- 1.** Donor screening procedures are part of the donor eligibility determination and are intended to establish that the donor:
  - a.** Is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases; and
  - b.** Is free from communicable disease risks associated with xenotransplantation.
- 2.** The manufacturer must screen a donor of cells or tissue by reviewing the donor's relevant medical records for:
  - a.** Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, including:
    - i.** Human immunodeficiency virus;
    - ii.** Hepatitis B virus;
    - iii.** Hepatitis C virus;
    - iv.** Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease;
    - v.** *Treponema pallidum*; and
  - b.** Communicable disease risks associated with xenotransplantation.
- 3.** Donors of viable, leukocyte-rich cells or tissue must be screened for the factors listed in section 2 and the manufacturer must also screen the donor of viable, leukocyte-rich cells or tissue by reviewing the donor's relevant medical records for risk factors for and clinical evidence of relevant cell-associated communicable disease agents and diseases, including Human T-lymphotropic virus.
- 4.** For donors of reproductive cells or tissue, medical records must be reviewed for risk factors for and clinical evidence of infection due to relevant communicable diseases of the genitourinary tract in addition to the relevant communicable disease agents and diseases listed in section 2 and 3 (for semen). Communicable disease agents of the genitourinary tract for which you must screen, unless they are recovered by a method that ensures freedom from contamination, include:
  - a.** *Chlamydia trachomatis*; and
  - b.** *Neisseria gonorrhoea*.
- 5.** Exceptions from the donor screening requirement are stated in 21 CFR 1271.90.
- 6.** If a complete donor screening procedure was done on a living donor within the previous 6 months, an abbreviated donor screening procedure may be used on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior.

During the inspection,

1. Determine the procedures in place to perform donor screening.
2. Determine if each donor has a separate and complete record of all relevant medical records.
3. Are the records available for review?
4. Verify that the medical records reviewed for donor screening are adequate to determine that the HCTP is free of risk factors for communicable disease.
5. Are the results and interpretation of the donor screening for communicable disease in compliance with 21 CFR 1271.75?
6. Is there documentation of the responsible individual performing the screening?



## ATTACHMENT C – DONOR TESTING

- A.** To adequately reduce the risk of transmission of relevant communicable disease all donors of HCT/Ps must be tested and found negative or nonreactive for the following:

HIV 1/2  
HBV  
HCV  
*Treponema pallidum*

- B.** In addition to testing for the disease agents listed in section **A**, donors of viable, leukocyte-rich cells or tissues (such as semen and hematopoietic stem/progenitor cells regulated solely under sec. 361) must also be tested for the following:

HTLV-I/II  
CMV (cytomegalovirus)

- C.** Donors of reproductive cells or tissue must be tested and found negative or nonreactive for the disease agents listed in section **A**, and the following:

1. Semen Donors:

HTLV I/ II  
CMV (cytomegalovirus)

2. Semen donors and donors of other reproductive cells or tissue (unless they are recovered by a method that ensures freedom from contamination):

*Chlamydia trachomatis*  
*Neisseria gonorrhoea*

**It should be noted that the following donors are exempt under 21 CFR 1271.90 from these testing requirements if the products are properly labeled: cells or tissue for autologous use, reproductive cells or tissue donated by a sexually intimate partner or cryopreserved cells or tissue for reproductive use subsequently intended for directed donation in certain circumstances.**

If the facility being inspected actually performs the communicable disease testing follow the guidance as appropriate in the “Guide to Inspection of Infectious Disease Marker Testing Facilities,” October 1996 [[www.fda.gov/ora/inspect\\_ref/igs/infdis.html](http://www.fda.gov/ora/inspect_ref/igs/infdis.html)]. For those facilities that do not perform testing on site verify required testing is being performed adequately through review of records on site, any written contracts, or agreements that exist.

During the inspection,

1. Determine that testing is performed using FDA-licensed, approved, or cleared donor screening tests. Verify that test kits used are for cadaveric specimens when appropriate and available.
2. Verify the laboratory performing the testing is certified under CLIA or has met equivalent requirements.
3. Determine that adequate samples are used for testing. In the case of a donor 1 month of age or younger, a specimen from the mother must be tested, all specimens for testing must be collected at the appropriate interval see 21 CFR 1271.80(b) and the establishment must evaluate the potential for plasma dilution and properly evaluate the sample.
4. Verify that test results are interpreted according to the manufacturer's instructions.
5. Observe actual testing or verify through record review that appropriate controls are used in testing, samples and controls are diluted properly, that the time and temperature of incubation are accurate and that instrument and equipment settings are correct during testing.
6. Verify that equipment maintenance is performed according to the manufacturer's directions and the firm's SOP.
7. Confirm that all testing problems are adequately investigated, resolved and documented.
8. Determine if all laboratory equipment is qualified, calibrated and maintained as required by user manuals, maintenance manuals and SOP's.
9. Ensure sample requirements specified in the product insert are met including: anticoagulant, age of sample, quantity, type of sample tube and storage temperature.
10. Verify that positive or reactive test results for relevant communicable disease agents are handled appropriately, and that HCT/Ps from ineligible donors are handled in accordance with 21 CFR 1271.65.

## ATTACHMENT D – PROCESSING AND PROCESS CONTROLS

Processing is defined in 21 CFR 1271.3(ff) as any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage and removal from storage. All HCT/P establishments must process each HCT/P in a way that does not cause contamination or cross contamination during processing, and that prevents the introduction, transmission or spread of communicable disease through the use of the HCT/P. When the results of processing cannot be fully verified later by inspection and/or testing, the firm must validate the process according to established procedures and demonstrate that the process consistently produces a result or that the HCT/P meets its predetermined specifications. Validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.

When changes are made to a validated process, the firm must review and evaluate the process, perform revalidation when appropriate, and document the activities.

During the inspection,

1. Determine which processes have been validated and which have been verified. .
2. Review process validation documentation and verification data
3. If the firm contracts out testing for microorganisms, how were the sampling and testing methods validated? Review any documentation of validation of sampling and testing methods
4. If the firm performs its own testing for microorganisms, review the documentation of the sampling and testing methods
5. Have changes to any validated processes been made?
  - a. Was the change documented?
  - b. Does the documentation include the relevant dates and signatures?
  - c. Was the process revalidated?
  - d. Was the change review and approved by the appropriate individual?
7. If the firm makes a written representation of sterility or viral inactivation, is there appropriate process validation or verification data to support the claim?

## ATTACHMENT E – LABELING

Requirements for labeling controls are in 21 CFR 1271.250. In addition, there are requirements for labels and labeling for nonreproductive HCT/Ps released for distribution in 21 CFR 1271.370. Requirements for records, which must accompany all HCT/P once an eligibility determination has been made, are in 21 CFR 1271.55.

Additional requirements for particular circumstances such as shipment of HCT/Ps from ineligible donors, HCT/Ps for which donor eligibility is not required and shipment of HCT/Ps for urgent medical need or shipment under quarantine are found in 21 CFR 1271.60, 1271.65 and 1271.90.

Report on the FDA 483, specific factual observations of deviations from the applicable labeling regulations for HCT/Ps as specified in 21 CFR 1271 (see revised IOM 512.01 Reportable Observations).

NOTE: Except for autologous, first or second-degree blood relatives, or directed reproductive donations, the accompanying records must not contain the donor's name or other personal information that may identify the donor such as name, social security number or medical record number.

During the inspection,

1. Determine the different circumstances under which the establishment has distributed HCT/Ps and determine if labeling procedures exist for each requirement and that the procedures are being followed.
2. Determine that all nonreproductive HCT/Ps are labeled with: (21 CFR 1271.370(b))
  - a. The identification code on the container,
  - b. A description of the HCT/P,
  - c. An expiration date if applicable, and
  - d. Any warning statements required.
3. For all nonreproductive HCT/Ps, does the procedure indicate the container label or the information accompanying the HCT/P includes 21 CFR1271.370(c):
  - a. The name and address of the establishment that determined the HCT/P met release criteria and made it available for distribution,
  - b. Storage temperature,
  - c. Other appropriate warnings,
  - d. Any instructions for use related to spread of communicable disease, and
  - e. A statement indicating if the donor is eligible or ineligible 21 CFR 1271.55(a)(2).
4. For all HCT/Ps where donor eligibility had been determined, establish that a summary of records accompanies the HCT/P and includes [21 CFR 1271.55(b)]:
  - a. A statement that the communicable disease testing was performed by a CLIA certified laboratory or equivalent,
  - b. A list and interpretation of all communicable disease testing performed,
  - c. Name and address of the establishment that made the donor eligibility determination,
  - d. If donor is ineligible and HCT/P was released under 21 CFR 1271.65(b) the reason the donor was determined to be ineligible.
5. For all HCT/Ps shipped under quarantine prior to the determination of donor eligibility the records that accompany the HCT/P must include [21 CFR1271.60(c)]:
  - a. The identification code on the container,
  - b. A statement that the donor eligibility has not been completed, and
  - c. A statement that the product must not be used until completion of the donor eligibility

determination unless the circumstances meet the exception noted for cases of urgent medical need.

6. An HCT/P made available for use under the exception for "urgent medical need" must be labeled as follows [21 CFR 1271.60(d)]:
  - a. A statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" and "WARNING: Advise patient of communicable disease risk" with the biohazard legend as in 21 CFR 1271.3(h) and
  - b. Information must accompany the HCT/P that includes the results of any required screening and testing that has been completed and a list of the required screening and testing that has not yet been completed.
  - c. Verify that the establishment notified the physician using the HCT/P that the screening and testing was not completed and that the donor eligibility determination was completed and the physician informed of the results during or after use of the HCT/P.
7. An HCT/P made available for use from an ineligible donor in compliance with 21 CFR 1271.65(b)(1) must be labeled as follows [21CFR 1271.65 (b)(2)]:
  - a. With the biohazard legend as in 21 CFR 1271.3(h) and a statement "WARNING: Advise patient of communicable disease risks,"
  - b. A statement of any reactive test results as follows: "WARNING: Reactive test results for (disease)" with the biohazard legend as in 21 CFR 1271.3(h) and
  - c. HCT/P must be accompanied by records required under 21 CFR1271.55.
  - d. Verify that the establishment notified the physician using the HCT/P of the results of testing and screening.
8. An HCT/P for nonclinical use from a donor determined to be ineligible may be used if labeled as follows [21 CFR 1271.65(c)]:
  - a. With the statement "For Nonclinical Use Only" and
  - b. With the Biohazard legend in 21 CFR 1271.3(h).
9. An HCT/P made available for use from a donor when donor eligibility was not required under 21 CFR 1271.90(a) must be labeled [21 CFR 1271.90(b)]:
  - a. "FOR AUTOLOGOUS USE ONLY" if appropriate,
  - b. "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" and "WARNING: Advise patient of communicable disease risks," if all required screening and testing has not been performed,
  - c. If appropriate, with the statement: WARNING: Advise patient of communicable disease risks," and
  - d. If appropriate, in the case of reactive test results the statements "WARNING: Reactive test results for (disease)" and include the biohazard legend as in 21 CFR 1271.3(h).

## **ATTACHMENT F – IMPORTS**

Any foreign manufacturer importing or offering for import HCT/Ps must be registered and list products with FDA pursuant to 21 CFR 1271.21. The foreign manufacturer may be contacted and apprised of the registration requirement if they intend to import HCT/Ps. Registration and listing may be done by submitting Form FDA 3356 via mail or electronically. Refer unregistered manufacturers to 21 CFR 1271.22 and the CBER Tissue Registration Monitor. Imported HCT/Ps are subject to the same requirements as domestically procured HCT/Ps.

The import provisions for HCT/Ps are found in 21 CFR 1271.420. If the imported HCT/Ps in domestic commerce are found to be in violation of 21 CFR 1271, the district may consider recommending issuance of an order of retention, recall and/or destruction (Refer to Part V of this program and RPM Chapter 5-6) or other regulatory/administrative action as appropriate. If violative HCT/Ps are still in import status, the district may consider detention and/or refusal.

If HCT/Ps are imported under quarantine only to undergo processing and then be returned to its country of origin with no distribution in the U.S., screening and testing for communicable diseases is not required. However, the HCT/Ps must be quarantined, accompanied by records assuring identification of the donor, and indicating that the HCT/Ps have not been determined to be suitable for implantation, transplantation, infusion, or transfer as required in 1271.60. The processor must follow the requirements in 1271.265 to ensure there is no infectious disease contamination or cross-contamination between the quarantined/untested foreign HCT/Ps and HCT/Ps that are intended for domestic distribution.

HCT/Ps imported for purposes other than in implantation, transplantation, infusion, or transfer, such as non-clinical research, or educational use are not subject to 21 CFR 1271, nor are they considered to be biological products subject to licensure in accordance with Section 351(a) of the PHS Act, nor are these products regulated as drugs or devices as defined in Section 201(g) and (h), respectively, of the FD&C Act. Therefore, FDA will not object to the entry or exportation of HCT/Ps not intended for transplantation for the stated purpose of non-clinical research, or educational use. HCT/Ps identified for further manufacturing into a device or device component are the responsibility of CDRH. Districts encountering such HCT/Ps should contact CDRH for guidance.

### **Exception for Imported Reproductive HCT/Ps**

The import requirements in 21 CFR 1271.420(a)&(b) do not apply to reproductive HCT/Ps, donated by a sexually intimate partner of the recipient for reproductive use, and regulated solely under section 361 of the PHS Act. Because a mechanism for determining whether imported reproductive HCT/Ps were donated by a sexually intimate partner of the intended recipient does not currently exist, it is impossible to verify compliance. Moreover, in some instances the intended recipients of imported reproductive HCT/Ps undergo preparatory treatment with gonadotropin therapy, which may have begun before importation takes place, and delays in the importation process may adversely affect the clinical treatment plan. Consequently, FDA must act promptly to facilitate receipt of imported reproductive HCT/Ps by the treating physician.

### **Exception for Peripheral Blood Stem/Progenitor Cells**

The import provisions in 21 CFR 1271.420(a)&(b) do not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act, except that paragraphs (a) and (b) apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission

which indicates the need to review the information referenced in 21 CFR 1271.420(a). If these HCT/Ps are encountered and the district believes that an unreasonable risk is associated with these products, OCBQ/DCM should be contacted (see Part VI for CBER contacts). Otherwise, CBER has determined that the medical needs of the recipients of imported hematopoietic stem cells derived from peripheral blood are of paramount importance, and the benefits to the recipients outweigh the risks. Consequently, FDA must act promptly to facilitate the release of imported hematopoietic stem cells for infusion to compromised recipients.

During the inspection,

1. Determine if the establishment receives imported HCT/Ps. If so, document the countries of origin and the approximate volume of imported HCT/Ps. In addition, document any problems related to imported HCT/Ps.
2. Determine if the foreign suppliers are registered with FDA. The list of registered firms is available at <http://www.fda.gov/cber/tissue/hctregistabl.htm>. If the firm is not shown on the website, contact the CBER Tissue Registration Monitor (see CBER Contacts in Part VI) to confirm their registration status.
3. If imported HCT/Ps are received, determine if the proper documents [i.e. accompanying records, including the summary of records required in 1271.55] are available for these products. Imported HCT/Ps (except imported reproductive HCT/Ps) must be labeled in accordance with 21 CFR 1271.370. Imported reproductive HCT/Ps must be labeled with appropriate warnings and statements in accordance with 21 CFR 1271.55, 1271.60, 1271.65, and 1271.90.

## ATTACHMENT G – CONTRACTORS

Many HCT/P establishments contract another establishment (e.g., a laboratory to perform communicable disease testing, a laboratory to perform microbiology cultures/ testing of HCT/P, or an irradiation facility to perform terminal sterilization) to perform work for them. Contractors that engage in only some operations subject to the CGTP regulations need only comply with those requirements applicable to the operations they perform. The contracting firm needs to:

1. Maintain the name and address and a list of the responsibilities of any contractor that performs a manufacturing step for them and this information must be available during inspection by FDA.
2. Ensure that the contractor complies with applicable CGTP requirements for the steps they perform. For example auditing a contract testing firm periodically is acceptable, as well as obtaining a written guarantee that the lab is complying with 21 CFR 1271.
3. If they become aware of information suggesting that the contractor may no longer be in compliance with such requirements, they must take reasonable steps to ensure the contractor complies with the requirements.
4. If the contractor is not in compliance with the requirements, the firm must terminate the contract, agreement, or other arrangement with the contractor.

During the inspection,

1. Determine the number and types of processes that are contracted out [e.g. recovery, testing, manufacturing,]
2. Determine if the contract firm has registered with FDA or if it is exempt.
3. How does the firm ensure that the contractor complies with the applicable CGTPs? Do they audit contractors?
4. Does the firm that determines donor eligibility have assurance that their contract laboratory is conducting the testing in accordance with 21 CFR 1271?
5. Is there a procedure for handling and reporting any deviations that occur at the contractor?
6. Does the firm have a process for handling a contractor that may no longer be in compliance with the CGTPs?



## ATTACHMENT H – REPRODUCTIVE TISSUE

Not all of the regulations in 21 CFR 1271 are applicable to reproductive cells or tissues. The applicable regulations include 21 CFR Part 1271 subparts A, B, C, F, 21 CFR 1271.150(c), and 21 CFR 1271.155 of subpart D for reproductive HCT/Ps described in 21 CFR 1271.10(a) and regulated solely under section 361 of the PHS Act.

Also, there are different requirements for donor eligibility determination and the other applicable HCT/P regulations depending on the relationship between the donor of the reproductive cells or tissue and the recipient: sexually intimate partner, directed reproductive donor [defined in 21 CFR 1271.3(l) as a donor of reproductive cells or tissue to a specific recipient, who knows and is known by the recipient before donation], or anonymous donor.

Establishments that recover reproductive cells and tissues are required to screen and test their donors for the communicable disease agents listed below, and in 21 CFR 1271.75 (a) and (b) and 21 CFR 1271.85 (a) and (b) unless exempted as in #2 (below) or unless they are recovered by a method that ensures freedom from contamination:

1. *Chlamydia trachomatis*
2. *Neisseria gonorrhoea*

Establishments must store or identify HCT/Ps from ineligible donors in a physically separate area, or follow other procedures, such as automated designation, that are adequate to prevent improper release until destruction or other disposition (21 CFR 1271.65(a)). Reproductive cells or tissue from a directed reproductive donor that has been determined to be ineligible based on the results of any screening or testing that may have been performed is not prohibited from use (21 CFR 1271.65(b)(1)(ii)).

The following regulations provide specific exceptions for reproductive tissue:

1. Establishments that recover reproductive cells or tissues and immediately transfer them into a sexually intimate partner of the donor are exempt from registration as per 21CFR 1271.15(e)
2. Establishments are not required to make a donor-eligibility determination under 21 CFR 1271.50 or to perform donor screening or testing under 21 CFR 1271.75, 1271.80 and 1271.85 for:
  - a. Cells and tissues for autologous use; or
  - b. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or
  - c. Cryopreserved cells or tissue for reproductive use, originally exempt under a or b above at the time of donation, that are intended for directed donation, provided that:
    - i. Additional donations are unavailable, for example, due to the infertility or health of a donor of the cryopreserved reproductive cells or tissue.
    - ii. Appropriate measures are taken to screen and test the donor(s) before transfer to the recipient.
3. Accompanying records as defined in 21 CFR 1271.55 (a)(1), in the case of autologous, first or second-degree blood relatives, or directed reproductive donations, may include an individual's name, social security number, or medical record number.
4. Reproductive HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use are exempt from the import provisions [21 CFR 1271.420 (c)].
5. As per 21 CFR 1271.440(f) FDA will not issue an order for the destruction of reproductive tissue under paragraph (a)(1) of this section, nor will it carry out such destruction itself under paragraph (a)(2) of this section.

During the inspection,

1. Determine if the firm has adequate procedures for determining eligibility of donors of reproductive cells and tissue.
  - a. Did the screening include review of the relevant medical records including the risk factors for and/or clinical evidence of genitourinary tract diseases?
  - b. Was the donor tested, where appropriate, for genitourinary tract diseases including *C. trachomatis* and *N. gonorrhoea*?
  - c. Are anonymous semen donors retested at least 6 months after the date of donation for evidence of infection due to relevant communicable disease agents?
2. Are the reproductive HCT/Ps adequately stored to prevent contamination and cross-contamination?
  - a. Are the reproductive HCT/Ps properly identified to relate the product to the donor and to all records pertaining to the product?
  - b. Are products from ineligible directed reproductive donors stored using a procedure adequate to prevent improper release?

## ATTACHMENT I – HEMATOPOIETIC STEM/PROGENITOR CELLS

**NOTE:** The regulatory framework for hematopoietic stem/progenitor cells (HPC) derived from peripheral or cord blood is dependent upon whether the product meets the criteria in 21 CFR 1271.10(a), and the intended use (i.e. the recipient) of the product.

- If the stem cell products are intended for unrelated allogeneic use (use in recipients unrelated to the donor), then the stem cell products are regulated under 351 of the PHS Act as drugs, devices and/or biological products, and are not intended for inspectional coverage under this program.
- If the stem cell products are intended for autologous use or for allogeneic use in a first or second degree blood relatives, and meet all of the other criteria in 21 CFR 1271.10(a), then the stem cell products are regulated under section 361 of the PHS Act and are covered under this compliance program.

Many HCT/P establishments that manufacture hematopoietic stem cells derived from peripheral or cord blood, manufacture these products for use in both allogeneic, and autologous, or allogeneic use in first or second-degree blood relatives, i.e. it is common for manufacturers to produce both HPCs regulated solely under PHS Act 361 and HPCs regulated under 351 of the PHS Act.

**HPCs derived from Peripheral Blood** are collected by an apheresis procedure after recombinant hematopoietic growth factor administration to the donor to increase the number of circulating stem/progenitor cells. Autologous donors may also have undergone chemotherapy mobilization to increase the number of circulating stem/progenitor cells in the peripheral circulation and increase the yield of the apheresis procedure. Peripheral blood stem/progenitor cell products are often infused in an unmodified state, but may be further processed. The most common procedures for processing allogeneic peripheral blood stem/progenitor cells are removal of ABO-incompatible red cells, removal of ABO-incompatible plasma, and cell selection to enrich the product with CD34+ cells and/or remove donor T lymphocytes. The most common procedures for processing autologous peripheral blood stem/progenitor cells are volume reduction by removing plasma prior to cryopreservation, cell selection to enrich the product with CD34+ cells, cryopreservation, and washing to remove the cryoprotectant DMSO after thawing. All of these procedures are considered minimal manipulation of the HPC product. Peripheral blood HPCs are most often refrigerated and administered within 24 hours of collection, but they may be cryopreserved. The cryoprotectant DMSO is considered to be a storage agent that, although unapproved for this indication, has a long history of use for storage of HPC products in liquid nitrogen and does not raise new safety concerns.

**HPCs derived from Cord Blood** are obtained by cannulation of the umbilical cord vessels at the time of delivery, after clamping of the cord and sterile preparation of the cannulation site. The placental blood drains by gravity into a receptacle containing an anticoagulant solution. Initial processing may include removal of red cells and plasma. The cells are usually cryopreserved for long-term storage. The final cryopreserved product volume generally ranges from 20-60 mL. Cord blood is a source of hematopoietic stem/progenitor cells, an alternative to bone marrow aspirates and peripheral blood apheresis products, for bone marrow reconstitution.

**HPCs collected from ineligible donors.** 21 CFR 1271.65(b)(1) allows the use of an HCT/P from an ineligible donor if the HCT/P is for allogeneic use in a first- degree or second-degree blood relative. This exception allows the physician and family to determine whether or not to use an HCT/P from a related donor who has been determined to be ineligible because the likelihood of finding an acceptable donor is greater among blood related individuals than among unrelated

individuals and in some cases survival rates of recipients may be better when transplanted with hematopoietic stem/progenitor cells from related donors.

**NOTE: The following description of “HPCs derived from Bone Marrow” is provided for informational purposes ONLY. These products ARE NOT HCT/Ps regulated solely under section 361 of the PHS Act. Health Resource Services Administration (HRSA) oversees bone marrow transplantation. See attachment A.**

**HPCs derived from Bone Marrow** are obtained through multiple needle aspirations from the posterior iliac crests and occasionally from the anterior iliac crests or sternum of an autologous or allogeneic donor. The marrow is placed in a sterile container with an electrolyte solution and anticoagulant. The cell suspension is passed through sterile filters to remove fat, bone particles, and cellular debris. The product volume varies with the weight of the recipient (10-15 ml/kg of donor weight), and generally ranges from 500 to 1500 ml. This HPC product contains mature red and white cells, platelets, committed precursors of all hematopoietic lineages, mast cells, fat cells, plasma cells, and pluripotent hematopoietic cells. Some of these constituent cells are capable of reconstituting the hematologic and lymphoid systems of an autologous or allogeneic recipient that has undergone myelosuppressive chemotherapy or radiation therapy, or both. This product usually undergoes further processing prior to infusion, similar to procedures for peripheral blood stem/progenitor cells, and may be cryopreserved for long-term storage in liquid nitrogen.

Minimally manipulated bone marrow for homologous use and not combined with a drug or device (except for a sterilizing, preserving, or storage agent, if the agent does not raise new clinical safety concerns with respect to the bone marrow) is not considered a HCT/P.

During the inspection,

1. Determine that specimens for communicable disease testing are collected in the appropriate time frame, which for peripheral blood stem/progenitor cells may be up to 30 days before recovery [21 CFR 1271.80(b)].
2. Determine that testing is performed for HTLV-I/II and CMV as hematopoietic stem/progenitor cells are considered leukocyte-rich cells [21 CFR 1271.85(b)].
3. Special attention should be paid to critical procedures for prevention of contamination of hematopoietic stem/progenitor cell products during manufacturing and prevention of cross-contamination, mix-ups and improper release, including:
  - a. Monitoring for temperature excursions during long-term liquid nitrogen storage
  - b. Validation of critical processes, e.g. volume reduction, cryopreservation
  - c. Strict compliance with SOPs for shipping from collection center to processing facility
  - d. Establishment and adherence to procedures for recovery, receipt and initial processing
  - e. Establishment of, and adherence to, procedures for tracking products and labeling controls

## ATTACHMENT J – RECORDS

HCT/P firms are required to maintain records for 10 years after creation unless otherwise stated in 21 CFR 1271.270. Records pertaining to a particular HCT/P must be retained at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest. Relevant medical records for donor eligibility as defined in 21 CFR 1271.3(s) must be in English or, if in another language, must be retained and translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document. The firm must establish and maintain a records management system relating to core CGTP requirements that allows for easy access and review. Records must be accurate, indelible, and legible. Records may be stored electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Firms must maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for them.

The firm must retain pertinent manufacturing records

During the inspection,

1. Any requirement in the CGTPs that an action be documented involves the creation of a record. Does the firm have relevant manufacturing records such as:
  - a. Equipment logs?
  - b. Labeling records?
  - c. Packaging records?
  - d. Are there any contract firm records and are they complete?
2. Are the records maintained, well organized, and readily available for review?
3. If records are stored electronically, how are they backed up?
4. Does the record identify the person performing the work?
5. Are entries dated and signed?
6. Are the records detailed enough to provide a complete history of the work performed?
7. Can the record be related to the particular HCT/P manufactured?
8. Are the donor eligibility records complete? [For information on Summary of Records, see attachment K] Do they contain:
  - a. Testing results and interpretation for relevant communicable disease agents in compliance with 21 CFR 1271.80 and 1271.85?
  - b. The name and address of the testing laboratory or laboratories?
  - c. Donor screening results and interpretation for communicable diseases in compliance with 21 CFR 1271.75?
  - d. The donor-eligibility determination, including the name and address of the establishment that made the determination?
  - e. Are the medical records in English or is there an English translation?
  - f. Does a statement of authenticity by the translator that specifically identifies the translated document accompany any English translations?

## ATTACHMENT K – SUMMARY OF RECORDS

The summary of records, used to make the donor-eligibility determination, is required by 21 CFR 1271.55 to accompany an HCT/P after the donor-eligibility determination is complete. The summary of records must contain the following information:

1. A statement that the communicable disease testing was performed by a laboratory:
  - a. Certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or
  - b. That has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services in accordance with those provisions;
2. A listing and interpretation of the results of all communicable disease tests performed;
3. The name and address of the establishment that made the donor-eligibility determination; and
4. In the case of an HCT/P from a donor who is ineligible based on screening and released under paragraph (b) of 21 CFR 1271.65, a statement noting the reason(s) for the determination of ineligibility.

The records must not contain the donor's name or any personal information that may identify them, except for autologous donations or donations from a directed reproductive donor. Records must be accurate, indelible, and legible. Medical records must also be in English or accompanied by a certified English translation.

During the inspection,

1. Review procedures for preparing the summary of records.
2. Determine if HCT/Ps that have completed the donor eligibility process are accompanied by a summary of records.
3. Are the records accurate, indelible, and legible?
4. Is the summary of records complete? Does the summary contain:
  - a. Testing results and interpretation for relevant communicable disease agents in compliance with 21 CFR 1271.80 and 1271.85?
  - b. Donor screening results and interpretation for communicable diseases in compliance with 21 CFR 1271.75?
  - c. The donor-eligibility determination, including the name and address of the establishment that made the determination?
  - d. Are the medical records in English or is there an English translation?
  - e. Does a statement of authenticity by the translator that specifically identifies the translated document accompany any English translations?
5. If the summary of records indicates the donor is ineligible, but the HCT/P is/was still being used does it meet one of the following criteria:
  - a. Is it for allogeneic use in a first or second-degree blood relative?
  - b. Is it a reproductive HCT/P from a directed reproductive donor as defined in 21 CFR 1271.3(l)?
  - c. Is there a documented urgent medical need as defined in 21 CFR 1271.3 (u)?