

# COMPLIANCE PROGRAM GUIDANCE MANUAL

## Imported Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)

### 7342.007 Addendum

Implementation Date:	Technical update *1/1/2015*
Completion Date:	*12/31/2017*
Product Codes:	57J Bone/Connective tissue (cartilage, ligaments, tendons)
	57K Semen/sperm, oocytes/eggs, embryos
	57L Eye tissue (cornea, sclera), amniotic membrane for eye repair
	57M Umbilical cord blood stem cells, peripheral blood stem cells, Lymphocytes (donor lymphocytes for infusion, T cells)
	57N Cell and Gene Therapies
	57P-99 Human Tissue, N.E.C.
	57Q Skin
	57R Veins, arteries
	57S Heart Tissue (heart valves, pericardium)
	57T Dura Mater

Program/Assignment Code: **42007**

### FIELD REPORTING REQUIREMENTS

All resources are planned under \*42007\*. Report accomplishments under appropriate PAC. Planned resources cover: PAC 42R833 (Entry Review), 41R824/42R824/45R824 (Follow-Up to Refusals), 99R833 (Filer Evaluations) and any inspections needed for PAC 42007.

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## **PART I – BACKGROUND**

FDA regulates certain human cells, tissues, and cellular and tissue-based products (HCT/Ps) under the legal authority of section 361 of the Public Health Service Act (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.

Three final rules are in effect regarding HCT/Ps:

- **Registration:** 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. [66 FR 5447]
- **Donor Eligibility:** On May 25, 2004, FDA promulgated regulations requiring most cell and tissue donors to be tested and screened for relevant communicable diseases. [69 FR 29786]
- **Current Good Tissue Practices (CGTPs):** On November 18, 2004, FDA issued regulations that require establishments that manufacture HCT/Ps to comply with 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. [69 FR 68612]

These final rules are contained in 21 CFR Part 1271. The new Part 1271 is made up of six subparts:

1. General provisions pertaining to the scope and purpose of Part 1271, as well as definitions.
2. Registration and listing procedures.
3. Provisions for the screening and testing of donors to determine their eligibility.
4. Current Good Tissue Practice (CGTP) requirements.
5. Certain labeling and reporting requirements.
6. Inspection and enforcement provisions.

These regulations apply to HCT/Ps recovered on or after the rule's effective date, May 25, 2005.

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 regulated solely under section 361 of the PHS Act. These HCT/Ps are subject to the regulations in 21 CFR 1271, and no pre-market approval is required. This compliance program encompasses only those HCT/Ps regulated solely under section 361 of the PHS Act.

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 in Part 1271, in addition to the regulations specific to drugs, biological products, or medical device and are not covered by this program.

## PART II – IMPLEMENTATION

This program provides information for making admissibility decisions regarding imported human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the PHS Act and regulations in 21 CFR 1271. 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 (21 CFR 1271.3(d)) and must be manufactured in accordance with the applicable provisions of 21 CFR Part 1271.

### A. Objectives

- To determine if the importer of record has met its obligation to provide sufficient information for FDA to make an admissibility decision, through an Affirmation of Compliance or otherwise.
- To facilitate the entry of imported products which meet these requirements, particularly hematopoietic stem cells and reproductive tissues where timing of patient care is critical.
- To determine the need to detain or refuse admission of HCT/Ps.

### B. Program Management Instructions

#### 1. HCT/Ps Covered by This Program [21 CFR 1271.3(d)]

HCT/Ps covered by this program include articles containing or consisting of human cells, or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples include, but are not limited to:

- Bone (including demineralized bone)
- Ligaments
- Tendons
- Eye/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

The HCT/Ps listed above 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<sup>1</sup>
- b. Intended for a homologous use only as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

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<sup>1</sup> Minimal manipulation means;

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

- 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.

The HCT/Ps listed below are covered by this program but entry of these products should be facilitated as described in section Part III.B.4.

- Hematopoietic stem cells derived from peripheral and cord blood (unless they may present an unreasonable risk to communicable disease transmission in which case 21 CFR 1271.420(a) & (b) apply)
- Semen (Sperm)
- Oocytes (Eggs)
- Embryos

## 2. Articles Not Covered by this Program

- a. Articles not regulated by FDA as HCT/Ps under 21 CFR Part 1271 [21 CFR 1271.3(d)]

The following are not regulated under 21 CFR Part 1271 as HCT/Ps and ***are not covered under this program***:

- **Vascularized human organs** for transplantation (kidneys, lungs, heart, liver, pancreas, including vascularized subparts of human organs) [HHS's Health Resources and Services Administration (HRSA) has oversight responsibility in this area];
- **Minimally manipulated bone marrow** [These products are regulated by Health Resources and Services Administration (HRSA)];
- **Whole blood or blood components or blood derivative products** [These products are regulated under section 351 of the PHS Act, the FD&C Act, and blood regulations, 21 CFR 600 – 680 and are required to be listed under 21 CFR Parts 607 and 207];
- **Secreted or extracted human products** such as milk, collagen, and cell factors (except that semen is considered an HCT/P);
- **Ancillary products** used in the manufacture of HCT/Ps;
- **Cells, tissues, and organs derived from animals other than humans**; and
- **In vitro diagnostic products as defined in 21 CFR 809.3(a)**. [These products are regulated by FDA as medical devices.]

- b. HCT/Ps that do *not* meet all criteria listed in 21 CFR 1271.10(a)

HCT/Ps that do not meet the criteria listed in 21 CFR 1271.10(a) are regulated as drugs, devices, and/or biological products under the FD&C Act and/or section 351 of the PHS Act. These HCT/Ps are subject to the regulations in Part 1271, in addition to the regulations specific to drugs, biological products, or medical devices. For examples of these HCT/Ps that do not meet all the 21 CFR 1271.10(a) criteria, see Attachment A, HCT/PS THAT DO NOT MEET ALL 21 CFR 1271.10(A) CRITERIA.

If you have questions about whether an imported HCT/P meets the criteria listed in 21 CFR 1271.10(a), call CBER, OCBQ, Division of Case Management (See Part VI. C. for contact information).

c. HCT/Ps Recovered Before May 25, 2005

Human tissues that were collected or recovered before May 25, 2005, are subject to 21 CFR 1270 and subparts A and B of part 1271, as appropriate, and not subject to Subparts C, D, E, and F, of 21 CFR 1271, the Donor Eligibility and CGTP final rule. Districts that have been processing entries of imported human tissues under 21 CFR 1270 may continue to use their existing procedures. If you have questions about processing entries that are subject to 21 CFR 1270, call CBER, OCBQ, Division of Case Management (See Part VI. C. for contact information).

3. Import sample collection and field examination

If CBER and the district determine that a physical sample should be collected, CBER will provide the necessary instructions (See Part IV Analytical).

Field examinations are performed, as appropriate, in accordance with established procedures. See IOM 6.4 “Field Examination.”

## PART III – INSPECTIONAL

### A. Import Requirement Exceptions from Entry Review Under 21 CFR 1271.420

Should these products come up for review, permit them to travel to the consignee under quarantine. FDA should act promptly to facilitate entry of the following products:

#### 1. Imported Reproductive HCT/Ps

Under 21 CFR 1271.420(c), the import requirements in 21 CFR 1271.420 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. This means that FDA would not expect to see an Affirmation of Compliance or other information regarding compliance with 21 CFR 1271 for these kinds of HCT/Ps when they are being imported or offered for import. Because an effective mechanism for determining whether imported reproductive HCT/Ps were donated by a sexually intimate partner of the intended recipient does not currently exist, FDA does not intend to review any entries of reproductive HCT/Ps at time of entry to verify compliance. 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 should act promptly to facilitate entry of imported reproductive HCT/Ps.**

#### 2. Hematopoietic Stem Cells

Under 21 CFR 1271.420(d), the import provisions in 21 CFR 1271.420 do not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act, except that when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease. FDA intends to treat stem cells from umbilical cord blood in a similar fashion. This means that FDA would not expect to see an Affirmation of Compliance or other information regarding compliance with 21 CFR 1271 for these kinds of HCT/Ps when they are being imported or offered for import unless such a risk existed. 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 are of paramount importance, and the benefits to the recipients outweigh the risks. **Consequently, FDA should act promptly to facilitate the entry of imported hematopoietic stem cells for infusion to compromised recipients.**

#### 3. Nonclinical Scientific or Educational Use

HCT/Ps imported by establishments that use them **solely** for nonclinical scientific or educational use are not subject to 21 CFR 1271 [21 CFR 1271.15(a)].

### B. Entry Review under 21 CFR 1271.420

Under 21 CFR 1271.420(a), the importer of record is required to: (1) notify the District Director (or his or her designee) that covers the port of entry before or at the time of importation and (2) provide “sufficient information for FDA to make an admissibility decision.” Entry reviewers should release the entry if it appears to be in compliance with the requirements of 21 CFR 1271. 21 CFR 1271.420 does not specify how importers of record should notify the districts, so notice may be given in several ways including paper or electronically through ABI and OASIS using an Affirmation of Compliance Code and qualifier (if a qualifier is required). Under

21 CFR 1271.420(b), HCT/Ps must be held intact by the importer of record or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The products should be permitted to travel to the consignee under quarantine while FDA is determining admissibility, due to the perishable nature of most HCT/Ps.

**NOTE:** Human tissues that were collected or recovered before May 25, 2005, are subject to 1270, and subparts A and B of part 1271, as appropriate. Districts that have been processing entries of imported human tissues under 21 CFR 1270 may continue to use their existing procedures (See Part II.2.c. for further information).

1. Affirmation of Compliance (AofC)

FDA establishes Affirmation of Compliance (AofC) codes that provide FDA district employees with information concerning the article offered for import. By using an AofC code, the filer affirms the product identified in an FDA line meets requirements specific to each code. AofC codes assist FDA in making admissibility determinations. Use of the AofC is voluntary, and may or may not provide for a more expeditious screening of the entry.

The AofC codes available for importers of HCT/Ps are outlined below.

a. HCT - HCT/P Compliant

This affirmation is used if the importer of record has determined that the HCT/Ps being imported or offered for import are in compliance with all applicable requirements of 21 CFR 1271 (e.g. applicable donor screening and testing, processing, and labeling). No qualifier is required when this AofC Code is transmitted.

AND,

b. HRN - HCT/P Registration Number

This affirmation is used if the establishment is registered with FDA. The qualifier required with use of this affirmation should be the HCT/P establishment registration number issued by FDA/CBER for the firm manufacturing the product identified in the FDA line. Most foreign manufacturers are required to register and submit a list of every HCT/P manufactured (21 CFR 1271.21), except those exempt from registration under 21 CFR 1271.15. For example, individuals (such as physicians) are not required to register or list if they are under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering and sending tissue to a registered establishment. Establishments that are exempt from FDA registration will not have a registration number and may not use this AofC.

The entry reviewer should verify the Affirmation of Compliance. The list of registered firms and product listings are available via the internet at <http://www.fda.gov/cber/tissue/tissregdata.htm>. If the firm or product is not shown on the website, contact the CBER Tissue Registration Coordinator (See Part VI.C for contact information), to confirm their registration and listing status.

If there appears to be no violation of the PHS Act or regulations, the reviewer should release the entry.

**NOTE:** Contact CBER/OCBQ/DCM if you encounter dura mater. See also IA-57-20, "Detention Without Physical Examination of Imported Dura Mater Regulated Under Section 361 of the Public Health Service Act."

**NOTE:** Contact CBER/OCBQ/DCM if you encounter HCT/Ps entries using the product code, 57P-99, Human Tissue, N.E.C., prior to making an admissibility decision.

## 2. Imported HCT/P's Intended for Further Processing

HCT/Ps that are imported for further processing and for distribution in the United States or for export are subject to 21 CFR 1271. Under 21 CFR 1271.265, shipments of HCT/Ps that are not available for distribution (“predistribution shipments”) must take place under pre-established criteria designed to prevent transmission of communicable disease and must be shipped under quarantine. Predistribution shipments must also comply with all other applicable requirements (e.g., labeling). Predistribution shipments must be shipped in quarantine. The “accompanying records” for a predistribution shipment may not yet be complete at the time FDA makes its admissibility decision, and that lack of completeness should not delay the FDA decision. The tissue establishment that later makes those tissues available for distribution is required to assure that the accompanying records are complete and other release criteria are met at the time it releases the tissues for distribution.

## 3. Documents that may be requested

If no Affirmation of Compliance is provided, or if questions relating to the entry arise, the entry reviewer may request relevant documents that provide sufficient information to make an admissibility decision. (As explained above in Part III.A. 1 & 2, *an affirmation of compliance should not be expected for entries of reproductive HCT/Ps and hematopoietic stem cells.*) Documents that may be requested include:

- a. “Accompanying Records” - donor eligibility records under 21 CFR 1271.55(a). Once a donor eligibility determination has been made, the following must accompany the HCT/P at all times. These records consist of:
  - i) A distinct identification code affixed to the container that links the HCT/P to the donor and to the HCT/P records [21 CFR 1271.55(a)(1)];
  - ii) A statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible [21 CFR 1271.55(a)(2)]; and
  - iii) A summary of the records used to make the donor eligibility decision [21 CFR 1271.55(a)(3) & 1271.55(b)]. “Summary of Records” includes [21 CFR 1271.55(b)]:
    - Statement that the communicable disease testing was performed by a CLIA-certified lab or the equivalent
    - List and interpretation of results of all communicable disease tests performed
    - Name and address of establishment making the donor eligibility determination
    - If the product is from an ineligible donor under 21 CFR 1271.65, a statement noting the reason for the ineligibility.
  - iv) The donor eligibility records 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 [21 CFR 1271.55(d)(2)].

Note: Exceptions to the requirements for a donor eligibility determination can be found at 21 CFR 1271.90

### b. Labeling as described in 21 CFR 1271.370:

- i) The following must appear on the product label of non reproductive HCT/Ps (i.e., these labeling requirements do not apply to semen, oocytes, and embryos):
  - The distinct identification code as assigned under 21 CFR 1271.290(c) [21 CFR

1271.370(b)(1)];

- A description of the type of HCT/P [21 CFR 1271.370(b)(2)];
- The expiration date, if any [21 CFR 1271.370(b)(3)]; and
- Warnings, under 21 CFR 1271.60(d)(2), 1271.65(b)(2), or 1271.90(b), if applicable and physically possible. If not physically possible to include on the label, warning must accompany HCT/P. [21 CFR 1271.370(b)(4)].
  - Product shipped in quarantine must be clearly identified as being in quarantine and be prominently labeled, “Not evaluated for infectious substances,” and “Warning: Advise patient of communicable disease risks.”
  - An HCT/P from an ineligible donor must be clearly labeled with the Biohazard legend with an additional warning statement to “Advise patient of communicable disease risks”.
  - In the case of reactive test results, a warning statement must be affixed stating “reactive test results”.
  - HCT/Ps must be clearly marked if “For Autologous Use Only” and include additional warning statements, where appropriate, as described above.

ii) The following must appear on the product label of non reproductive HCT/Ps or must accompany the product:

- Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution [21 CFR 1271.370(c)(1)];
- Storage temperature [21 CFR 1271.370(c)(2)];
- Other warnings, where appropriate [21 CFR 1271.370(c)(3)]; and
- Instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases [21 CFR 1271.370(c)(4)].

#### 4. Status of product while an admissibility decision is made.

Under 21 CFR 1271.420(b), the product must be held intact by the importer of record or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The product may travel to consignee under quarantine while FDA is determining admissibility due to perishable nature of HCT/Ps.

#### 5. Counterfeit HCT/Ps

If you suspect that an imported HCT/P is counterfeit, contact CBER/OCBQ/DCM to establish an appropriate plan of action.

#### 6. American Goods Returned

If an imported HCT/P has been returned (American Goods Returned), rejected, or has a complaint file, the district should carefully review that entry to determine the reason for the return, rejection, or complaint. Such HCT/Ps are imported products and must meet all appropriate requirements of 21 CFR 1271. In addition, such HCT/Ps identified as American Goods Returned should travel with documentation demonstrating that product was kept under the appropriate storage conditions while in foreign storage and during shipment back to the United States. In your judgment, if there is reason to believe that an appearance of violation may exist, then consult with CBER/OCBQ/DCM for assistance, if needed. HCT/Ps should be

detained with the appropriate charge when they appear violative. If there are any questions, contact CBER.

7. Severe Health Threat

In *rare* circumstance where a severe health threat may exist, FDA may examine and/or sample the HCT/P. In such a circumstance, the HCT/P should be held in quarantine. If a situation involving a severe health threat occurs, CBER is responsible for notifying CDC, as appropriate, in accordance with existing procedures.

Attachment A – [HCT/Ps THAT DO NOT MEET ALL 21 CFR 1271.10\(A\) CRITERIA](#)

#### **PART IV – ANALYTICAL**

If sample collection is necessary, specific instructions will be provided, including the laboratory or laboratories to which the sample should be sent. Consult with CBER program contacts identified in Part VI, *before* collecting samples for agency analysis, except for documentary samples for interstate commerce (see IOM 4.1.4.2 \*and 4.4.6.2.1\*) to support regulatory or administrative action). When sample collection is necessary, CBER will notify the Medical Products and Tobacco Scientific Staff, Office of Regulatory Science, Office of Operations/ORAs.

If samples are to be evaluated by CBER, contact the CBER Sample Custodian (\*240-402-9165\*) before shipping any samples. No one is available to receive samples over the weekend. Ship all samples collected under this program to:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Sample Custodian (FEI No. 100038447)  
10903 New Hampshire Avenue  
WO75 – G707  
Silver Spring, MD 20993-0002

Collect \*and ship\* any samples of a potentially bio-hazardous nature in accordance with IOM 1.5.5 \*and 4.5.5.8.6\*.

CBER will forward results to the home district of the involved facility, with a copy to CBER, OCBQ, Division of Case Management (DCM). Investigators should document in FACTS or to whom CBER should send the sample results. If unable to document in FACTS, use Form FDA-464a, Collection Report Continuation Sheet.

Submit copies of collection reports for physical samples to CBER, OCBQ, DCM.

## PART V - REGULATORY/ADMINISTRATIVE STRATEGY

For violative imported HCT/Ps regulated solely under section 361 of the PHS Act and 21 CFR 1271, that are still in import status, the enforcement options available include:

Detention	<p>Detain product and allow reconditioning, if applicable, (FDA-766). See RPM Chapter 9, Subchapter Reconditioning.</p> <p>Include the following statement on the Notice of FDA Action: "This Human Cell, Tissue, and Cellular and Tissue-Based Product is in violation of section 361 of the Public Health Service Act. [PSQI 361] (OASIS Charge Code = 361 HCT/P)."</p>
Refusal	<p>Refusal of HCT/P based on violations of 21 CFR 1271. HCT/P can be re-exported or destroyed.</p>
Detention Without Physical Examination (DWPE) – Import Alert	<p>Districts may recommend DWPE whenever there is information that would cause future shipments of HCT/Ps offered for entry to appear violative under 21 CFR 1271. See RPM Chapter 9, Subchapter Detention Without Physical Examination, regarding procedures for DWPE and other pertinent guidance on entry control procedures.</p> <p>Recommendations for DWPE should be referred to CBER, Division of Case Management, HFM-624, through ORA/ORO, Division of Import Operations and Policy, HFC-170.</p>
Warning Letter	<p>See RPM Chapter 9, Subchapter Priority Enforcement Strategy for Problem Importers.</p> <p><b>NOTE:</b> There is no direct reference authority for the issuance of these Warning Letters.</p>
Bond Actions	<p>Bond actions may be initiated by Customs and Border Protection (CBP) when an entry is distributed prior to FDA release and cannot be redelivered, or when an article has been detained and refused and the article is not destroyed or exported in accordance with the requirements of the law. Districts should work closely with the responsible CBP office. See IOM 6.2.7.11 Bond Actions and RPM Chapter 9, Subchapter Bond Actions.</p>
CBP Seizures	<p>CBP has seizure authority over merchandise whose importation or entry is subject to any restriction or prohibition which is imposed by law relating to health or safety and may be seized in accordance with 19 USC 1595a(c)(2)(A). Provide CBP with charge code, pertaining to health or safety.</p>

## **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), [21 CFR Part 16](#), Regulatory Hearing Before the Food and Drug Administration
- [21 CFR Part 1271](#), Human Cells, Tissues, and Cellular and Tissue-Based Products
- [Tissue Proposed & Final Rules](#)
- [Human Cell and Tissue Establishment Registration Public Query](#)
- [Investigations Operations Manual](#) (IOM), Chapter 6 - Import
- IOM, Chapter 6 – 6.4.6 - Field Examinations – Biologics
- [Regulatory Procedures Manual, Chapter 9 - Import Operations/Actions](#)
- [Form FDA 3356, Establishment Registration and Listing for Human Cells, Tissues and Cellular and Tissue-Based Products \(HCT/Ps\)](#)
- [\\*Importing CBER-Regulated Products into the United States\\*](#)

### B. Program Contacts

General import compliance issues:

#### **CBER**

#### **OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY**

**Division of Case Management**, Robert Sausville, Director

Phone: 240-402-9155

Fax: 301-595-1302

Kimberly Cressotti: 240-402-8916

Marc Alston: 240-402-8879

\*Jessica Dunn: 240-402-8985\*

#### **OFFICE OF CELLULAR, TISSUE AND GENE THERAPIES**

**Division of Human Tissue**, CAPT Ellen Lazarus, M.D., Director

Phone: 240-402-8325

Fax: 301-595-1303

Rosemarie Wiseman, CBER Tissue Registration Coordinator: 240-402-8369

#### **ORA/OFFICE OF ENFORCEMENT AND IMPORT OPERATIONS**

**Division of Import Operations**, HFC-172

Phone: 301-796-0356

FAX: 301-827-4086

Stella Notzon: 301-796-6678

\*Malinda Shelman: 360-332-2681\*

\*Anthony Nicoli: 612-758-7150\*

**ORA/OFFICE OF REGULATORY SCIENCE**

\*Medical Products and Tobacco Scientific Staff, George Salem

Phone: 301-796-6111

Fax: 301-827-9806\*

## **PART VII – CENTER RESPONSIBILITY/PROGRAM EVALUATION**

CBER/OCBQ will work cooperatively with ORA, and the Biological Products Field Committee, concerning imported HCT/Ps covered under this compliance program.

The ORA annual workplan, developed by CBER and ORA, provides overall resource allocations. However, in rare circumstance where violations exist that pose a severe health threat, FDA may examine and/or sample the HCT/P, which may result in unplanned import activities taking more or less time than estimated in the workplan. In such a circumstance, the HCT/P should be held in quarantine and the Center should be contacted for further guidance.

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, and regulations.

CBER/OCBQ will continue to use accomplishment data from the ORA OASIS, ORADSS Import Systems, and Field Accomplishment and Compliance Tracking System (FACTS), requests for policy decisions/clarification received from the public or the industry, and input from CBER scientific and product experts to aid industry and the field in the development of a consistent import compliance program that meets all applicable HCT/P regulations.

## **ATTACHMENT A – HCT/Ps THAT DO NOT MEET ALL 21 CFR 1271.10(A) CRITERIA**

HCT/Ps that do not meet the criteria listed in 21 CFR 1271.10(a) are regulated as drugs, devices, and/or biological products under the FD&C Act and/or section 351 of the PHS Act. These HCT/Ps are subject to the regulations in Part 1271, in addition to the regulations specific to drugs, biological products, or medical devices.

If it is unclear how the HCT/P offered for import is regulated, contact CBER for clarification or guidance (see CBER contacts in Part VI.).

### **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](#)
- Gene therapy products
- [Human cloning](#)
- [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)
- Unrelated allogeneic hematopoietic stem cells
- Unrelated donor lymphocytes for infusion.

### **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