Current Good Tissue Practice  
Basics for Human Cells, Tissues, and Cellular and Tissue-Based Products  

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This article reviews the current good tissue practices and regulations governing human cells, tissues, and cellular and tissue-based products. A regulation background and an overview of quality systems and the reporting of deviations and adverse events are presented.

INTRODUCTION

The purpose for regulations governing human cells, tissues, and cellular and tissue-based products (HCT/Ps) is to prevent the introduction, transmission, and spread of communicable disease (1,2,3). HCT/Ps are regulated under 21 Code of Federal Regulations (CFR) 1271 and section 361 of the Public Health Service (PHS) Act. Some HCT/Ps are also regulated as drugs, devices, and/or biologics under section 351 of the PHS Act, 21 CFR 1271.20, and applicable sections of 21 CFR (2).

Manufacturers of HCT/Ps are inspected by the Center for Biologics Evaluation and Research (CBER), with the number of inspections having increased from 111 in 1998 to 383 in 2008 with an average inspection time in 2008 of approximately 40 hours. Approximately 75% of the inspections conducted in 2008 resulted in “No Action Indicated” (NAI), 23% resulted in “Voluntary Action Indicated” (VAI), and the remaining 2% in “Official Action Indicated” (OAI) (4). The high percent of inspections resulting in NAI demonstrates that manufacturers understand the requirements, have established the necessary programs and controls, and are complying with the regulations.

21 CFR 1271.10(a) describes the criteria for the risk-based categorization of products; whether products are regulated under section 361 of the PHS Act and 21 CFR 1271 or if the products are regulated as drugs, devices, or biologics under section 351 of the PHS Act, 21 CFR 1271.20, and applicable sections of 21 CFR (2).

A product is regulated under section 361 of the PHS Act if the product meets all of the following criteria (3):

- “The HCT/P is minimally manipulated
- “The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent
- “The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P
- “Either:
  - The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
  - The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
    - Is for autologous use
    - Is for allogeneic use in a first-degree or second-degree blood relative, or
    - Is for reproductive use” (3).

Some examples of products that meet the criteria for section 361 HCT/Ps and are minimally manipulated, intended for homologous use only, and are not combined with another article (with some exceptions) include:
bone, cartilage, peripheral or umbilical cord blood, skin, heart valves, and reproductive cells and tissues (e.g., semen, oocytes, embryos) (2).

Prior to the effective date of the final rule, tissue was still being processed. It was therefore necessary for the US Food and Drug Administration to clarify when and how the final rule would apply to tissues processed prior to the effective date of the final rule. Therefore, FDA specified that HCT/Ps recovered on or after May 25, 2005 were subject to the regulation in 21 CFR 1271 and if the tissue was recovered prior to May 25, 2005, the tissues are regulated under 21 CFR 1270 (5).

If the product is categorized as a “361 Product,” the establishment that performs a manufacturing step or performs the step under contract for another HCT/P establishment must register with FDA, must submit a list of each HCT/P product manufactured, and must comply with 21 CFR 1271 (3). “361 Products” are not required to be licensed, approved, or cleared under a premarket notification (5).

Establishments with products regulated as drugs, devices, or biologics under section 351 and/or the FD&C Act must also register and list their products (3). Establishments that manufacture a drug and/or device under an investigational new drug application (IND) or an investigational device exemption (IDE) are not required to register and list their product until the product is approved or cleared (2). Products regulated under section 351 (not meeting the requirements in section 361) require FDA premarket review and a license, approval, or clearance (5).

BACKGROUND
Initially the approach to regulating human cellular and tissue-based products was not well organized, highly confusing, and lacked consensus. In 1997, FDA proposed a new strategy for the risk-based approach for regulating these products. This risk-based approach regulated some products under the PHS Act and others as drugs, devices, or biological products under the FD&C Act. FDA proposed the following three final rules and two interim rules to support this risk-based approach:
- “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (registration final rule) (66 FR 5447, January 19, 2001). This rule introduced definitions and registration/listing procedures. The first phase applied to establishments and products already regulated under section 361 and 21 CFR 1270. The second phase applied to products regulated as devices, drugs, or biologics; hematopoietic stem cells from peripheral and cord blood, and reproductive cells and tissues. The second effective date was January 21, 2004.
- “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (interim final rule) (66 FR 3823, January 27, 2004). This interim rule exempted human dura mater and human heart valve allografts from the definition of HCT/Ps and became effective January 23, 2004 with a compliance date of March 29, 2004.
- “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products” (donor eligibility final rule) (69 FR 29786, May 25, 2004). This final rule established the requirements for screening and testing donors with an effective date of May 25, 2005.
- “Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments, Inspection, and Enforcement” (CGTP final rule) (69 FR 68612, November 24, 2004). This final rule established the current good tissue practice (CGTP) requirements and became effective on May 25, 2005.
- “Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling” (interim final rule) (70 FR 29949, May 25, 2005). This interim final rule revised regulations for screening and testing of HCT/P donors and related labeling. The effective date was May 25, 2005 (2).

On June 19, 2007 (72 FR 33667), FDA adopted as a final rule the May 25, 2005 interim final rule without any changes (2).

CURRENT GOOD TISSUE PRACTICE REQUIREMENTS
Current good tissue practices are the requirements set forth in 21 CFR 1271 subparts C and D that gov-
ern methods used in and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution (3,6). The primary requirements for compliance with the CGTPs are focused on the prevention of the introduction, transmission, or spread of communicable disease by HCT/Ps. Therefore, there is heavy emphasis on environmental control programs which encompass facility design, personnel and material flow, cleaning procedures, training of personnel, control of components, processing controls, changeover procedures, as well as donor screening and testing.

Specifically, the CGTP core requirements apply to operational areas and operations performed including the following, as applicable:

- Facilities
- Environmental control
- Equipment
- Supplies and reagents
- Recovery
- Processing and process control
- Labeling controls
- Storage
- Receipt, predistribution shipment, and distribution
- Donor eligibility determination, screening, and testing
- Support activities (e.g., record management, and other requirements as outlined in 21 CFR 1271.150(a)) (1,3).

If the establishment contracts to another establishment to perform any step in the manufacturing process, there are requirements to ensure that there is a contract or other written agreement for the responsibilities transferred to the contract establishment. It is the responsibility of the manufacturer to ensure the contract facility is compliant with all applicable CGTP requirements. Oversight of the contract facility should include the following:

- Ensure responsibilities are clearly understood
- Review test methods and procedures used by contractor
- Review standard operating procedures
- Verify certifications
- Review inspection reports issued by regulatory agencies
- Conduct data audits
- Conduct audits of the quality system.

If during the oversight of the contract establishment it becomes known that the contract establishment is not fulfilling CGTP requirements, steps must be taken to investigate the cause of noncompliance, evaluate potential risk, assign corrective and preventive action, and verify effectiveness of those actions taken.

When HCT/Ps are classified as 351 or 361 Products, CGTPs as well as CGMP requirements apply (e.g., 21 CFR 210-211, 21 CFR 820 as applicable). If regulated as a biological product, those CGTP requirements not covered under CGMP must be followed, including but not limited to the following:

- Donor eligibility
- Prevention of potential introduction, transmission, or spread of communicable disease
- Manufacturing agreements
- Audits
- Prohibition of pooling
- Predistribution shipment
- Packaging and shipping requirements
- Record keeping for 10 years
- Traceability (1).

For HCT/P products regulated as medical devices 21 CFR 820 is applicable in addition to CGTPs because all requirements are not included in the quality system defined in 820. The following are examples:

- Donor eligibility
- Prevention of potential introduction, transmission, or spread of communicable disease
- Manufacturing agreements
- Prohibition of pooling
- Predistribution shipment
- HCT/P availability for distribution only after donor eligibility has been established
- Packaging and shipping requirements
- Record keeping for 10 years; cleaning records for three years
- Certain records for contracts and agreements
- Traceability (1).
QUALITY SYSTEM FOR HCT/PS
The quality system must ensure that procedures relating to good tissue practice requirements are established and maintained. Required procedures include those for receiving, investigating, evaluating, and documenting information about contamination, potential contamination, or potential communicable disease transmission with other establishments (3,4). Additionally, the quality system must include requirements for management oversight of the quality system, definition of the quality assurance function roles and responsibilities, including the audit and/or monitoring function, definition of the purchasing control program including supplier management, and the corrective and preventive action program as well as other subparts of the CGTP regulation. An establishment that performs any step in the manufacture of HCT/Ps must establish and maintain a quality program that is appropriate for the manufacturing steps performed and the specific HCT/P manufactured (3,4).

The quality program must ensure that the establishment complies with the requirements of the applicable CGTP requirements. These requirements include the following:

- Personnel
- Written procedures
- Facilities
- Equipment maintenance and calibration
- Reagents and supplies
- Environmental controls
- Donor eligibility
- Production and process control
- Process changes
- Process validation
- Labeling controls
- Storage
- Receipt, predistribution shipment, and distribution
- Labeling
- Tracking
- Audits
- Software verification and validation
- Complaint handling
- Corrective and preventive action
- Recordkeeping.

Personnel
Personnel must be adequately qualified and properly trained to perform their assigned tasks. Personnel involved with the processing of HCT/Ps must have job descriptions defining their responsibilities and assignments and defining basic job requirements. The individual responsible for supervising personnel must identify the job requirements and ensure personnel are adequately qualified and trained for the position to which they are assigned. Personnel must only be assigned to tasks for which they are trained. Qualification may include prior experience, education, or certification. Qualifications and completed training must be documented (1,3).

Written Procedures
Procedures must be established and followed for all aspects of the quality system. The procedures should be written in such a manner to minimize potential for misunderstanding by individuals who will be using the procedures. Procedures must be reviewed and approved by individuals knowledgeable in the subject matter described in the procedure. When there are changes to procedures, the changes must be reviewed and approved prior to implementation. Once procedures are established the procedures must be available to users and consistently followed (1, 3). Procedures must define the process for sharing information with other establishments that are known to have recovered HCT/Ps from the same donor and with establishments that are known to have performed manufacturing steps on the same HCT/P (1,3).

Facilities
Facilities must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-up (1,3). Other requirements are consistent with CGMP for medical devices and drugs with regards to the lighting, ventilation, general air quality, plumbing, utilities, drainage system, and general state of repairs. Cleaning procedures must be in place to minimize the potential for contamination. Environmental monitoring (e.g., viable, nonviable, surface, personnel, and air monitoring) is required to determine the effectiveness of the cleaning, efficiency of the air filtration,
and personnel practices. The facility must be designed to minimize potential risk of contamination, with adequate separation of activities and appropriate directional flow of personnel, material, waste, and product (1,3).

**Equipment Maintenance And Calibration**

Equipment must be of appropriate design for its intended use and must be qualified to ensure valid results are obtained. Equipment cleaning procedures must be in place to ensure there is a minimum potential for contamination and/or cross contamination. Equipment must be maintained and calibrated at regular intervals. Equipment such as biological safety cabinets and laminar flow workstations must be certified at sufficiently frequent intervals to ensure the units operate as intended. It is especially important to identify the appropriate cabinet or workstation for the intended work and level of personal and product protection required. Maintenance and calibration records as well as qualification and cleaning validation records are required to be maintained. It is a requirement that procedures for cleaning, sanitizing, and maintaining equipment be in place as described in 21 CFR 1271.200(b). If contract facilities are utilized for equipment cleaning and/or maintenance, adequate oversight must be in place and documented. Contract facilities are considered an extension of your own establishment and must comply with the same requirements as those that apply to your establishment (1,3).

**Reagents And Suppliers**

As defined in 21 CFR 1271.210, supplies and reagents must be verified as having met their specifications prior to use in order to minimize the potential for contamination and/or cross contamination. The verification of conformance to specifications may be performed by the facility utilizing the material or by the supplier. In regards to in-house testing performed, certificates of analysis and other associated technical and conformance information obtained, including any process validation data, may be used to qualify the supplier and the materials provided by that supplier. Reagents and supplies must be handled and stored using the manufacturer’s recommendations. If reagents are produced in-house, the process must be validated or verified. Records of incoming supplies and reagents must be maintained documenting the receipt, description of material, quantity, manufacturer, catalog or part number, lot number, date of receipt, and expiration date, as appropriate for the material received. Records of the steps taken for verification of performance to specifications must be maintained. Records must be maintained of the specific lots of material used linking the lot of material to the processing of each HCT/P (1,3).

**Environmental Controls**

Controls must be established to minimize the potential for contamination, including the following where appropriate:

- Temperature
- Humidity
- Ventilation
- Air filtration
- Pressurization with positive pressure from clean to less clean areas
- Cleaning and disinfection with appropriately determined agents
- Equipment maintenance
- Biological safety cabinets
- Use of closed systems
- Periodic inspection of control systems (1,3).

**Donor Eligibility**

A determination must be made as to whether a donor is eligible for donating cells or tissue for use as a HCT/P. The determination is based on both donor screening and donor testing. Medical records must be reviewed for evidence of risk factors and or clinical evidence of relevant communicable diseases listed in 21 CFR 1271. The relevant communicable diseases have been selected based on risk of transmission, severity of effect, and availability of appropriate screening measures or tests (6). Interviews with the donor are also used during screening along with written questionnaires. Risk factors or conditions used for screening include but are not limited to the following:

- Men who have had sex with men in the preceding five years
- Persons who have injected drugs for non-medical reasons in the preceding five years
- Persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates in the preceding five years
• Persons who have engaged in sex in exchange for money or drugs in the preceding five years
• Persons who have had sex in the preceding 12 months with any person described above or with any person who has HIV infection, including a positive or reactive test for HIV
• Persons who have been exposed in the preceding 12 months to known or suspected HIV-, Hepatitis B virus (HBV)-, and/or Hepatitis C virus (HCV)-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane
• Children born to mothers with or at risk for HIV infection if 18 months or younger or if breast-fed within the preceding 12 months
• Persons who have been in juvenile detention, lock up, jail, or prison for more than 72 consecutive hours in the preceding 12 months
• Persons who have lived with another person who has Hepatitis B or clinically active Hepatitis C infection in the preceding 12 months
• Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 12 months, in which sterile procedures were not used
• Persons who have had a past diagnosis of clinical symptomatic viral hepatitis after their 11th birthday unless evidence from the time of illness documents that the hepatitis was identified as being caused by Hepatitis A virus, Epstein-Barr (EBV), or Cytomegalovirus (CMV)
• Persons who are diagnosed and have a documented medical diagnosis of sepsis or have document clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death
• Persons who have had a Smallpox vaccination in the preceding eight weeks
• Persons who have had a medical diagnosis or tested positive or reactive to West Nile virus or have been diagnosed with or at increased risk of vCJD
• Persons who have been treated or had Syphilis within the preceding 12 months
• Additional risk factors are listed in reference 7 along with a description of clinical symptoms to be considered during donor screening (3,7).

Laboratories used for donor testing must comply with specified requirements as defined in 21 CFR 1271.1, 1271.80. Laboratories must be FDA licensed, use tests that are labeled for cadaveric specimens and be FDA licensed, approved, or cleared for donor screening, and the laboratory must be Clinical Laboratory Improvement Act (CLIA) certified or meet equivalent requirements by the Center for Medicare and Medicaid Services. Assays must be performed and interpreted according to the manufacturer's instructions (3,7).

Required donor testing includes testing for HIV-1, HIV-2, HBV, HCV, Syphilis, and HIV p24 antigen. Additional tests required for donors of viable, leukocyte-rich cells or tissues (e.g., hematopoietic stem, progenitor cells, semen) include the following: Human T-lymphotropic Virus Type I and II and Cytomegalovirus (3,7).

Additional screening and testing requirements have been defined for donors of reproductive cells and tissues and these are found in reference 7 and 21 CFR 1271.75, 1271.80, and 1271.85.

Production And Process Control
Establishments that recover HCT/Ps must register with FDA and establish procedures that describe the operations performed at their facilities and procedures related to those operations including: facilities, environmental controls, equipment, supplies and reagents, labeling controls, storage, and receipt, predistribution shipment, and distribution of HCT/Ps. A quality system must be in place to address all of the CGTP requirements that are applicable to the work conducted at that establishment. In addition, steps must be taken that ensure there is a minimal potential for contamination and/or cross contamination. Steps should include the establishment of an effective environmental control program with trained personnel, adequate cleaning and sanitation procedures, appropriately designed facilities, etc. Donors must be stringently screened to ensure donor eligibility and a mechanism for tracking the material throughout the process must be in place to prevent the spread of communicable disease agents. Processing records should be periodically verified against recovery records to ensure there is complete traceability from the donor to the processed HCT/P (1,3).
Processing of all HCT/Ps must be performed in a manner to minimize the potential for contamination and/or cross contamination. Human cells or tissue from two different donors must not be pooled (e.g., placed in physical contact or mixed in a single receptacle) during manufacturing as defined in 21 CFR 1271.220(b). Although the regulation does not prohibit the pooling of HCT/Ps processed from the same donor, this practice is discouraged because products processed at different times may increase the risk of contamination or cross contamination (1,3).

In-process and final tests must be established to ensure the processing and release of HCT/Ps meet established specifications. Test and inspection steps must be carefully selected for critical control points and test methods must be identified that are appropriate for the process step to be evaluated. Included in the test and inspection steps must be a pre-processing microbiological culture. The results from these cultures must be included in the evaluation for release of material (1,3).

Sterilization, disinfection, and aseptic processes must be validated according to standard industry practice. Although there is no requirement for HCT/Ps to be sterile, the products must be recovered, processed, and handled aseptically (1,3).

**Process Changes**

Process changes in the recovery or processing of HCT/Ps must be handled just as changes are handled with drug and medical device products. Any process change requires verification or validation depending on the type of change and process. The change must be evaluated for its potential impact, especially for the potential for contamination and/or cross contamination when working with HCT/Ps. The change must be reviewed and approved prior to implementation, and the change must be documented according to established change control procedures (1,3).

**Process Validation**

When a process cannot be verified by subsequent inspection and test, the process must be validated as required by 21 CFR 1271.230. Similar to requirements for drugs, biologics, and medical devices, the validation requires a pre-approved protocol with established acceptance criteria. The work performed in support of the validation must be documented along with conclusions in a final report. The final report must be reviewed and approved. When changes are made to a validated process, the change must be reviewed and evaluated and a revalidation performed where appropriate. Changes that require revalidation include: type of antibiotic used in a processing reagent, concentration of a reagent used for processing, amount of time that an HCT/P is exposed to a reagent, temperature during processing, and lyophilization cycle that could potentially cause contamination or cross contamination (1,3).

**Labeling Controls**

Procedures must be established and maintained as described in 21 CFR 1271.150 to control the labeling of HCT/Ps. HCT/Ps must be labeled at all times to ensure their identification and to minimize the potential for mix-up. Each step of processing must include verification of labeling; including an inspection for accuracy, legibility, and integrity (1,3).

**Storage**

Storage areas must be designed and maintained to prevent mix-ups, contamination, and cross contamination of HCT/Ps, supplies, and reagents; and prevent the potential for distributing a HCT/P prior to release. Areas within the storage area must be designated for quarantine, rejected, and approved materials. Within approved areas there must be signage (or similar) stating the type of material stored in that area. This signage and designated storage location help to minimize the potential for mix-up. Prior to release of HCT/Ps for distribution, the HCT/P must be well labeled as quarantined and maintained in a quarantine area until all requirements have been successfully met. Automated control may be used provided the computerized system has been validated. HCT/Ps must be stored at an appropriate temperature to minimize potential adverse effects during storage. To determine the appropriate storage conditions, guidelines from professional organizations can be used or alternatively, studies may be conducted internally to determine the appropriate storage conditions. Expiration dates must be assigned to HCT/Ps based on HCT/P type, processing includ-
ing the method of preservation, storage conditions, and packaging. If there is a deviation in storage conditions, appropriate corrective and preventive actions must be taken and documented. If the excursion may potentially cause contamination, the HCT/P must be discarded or otherwise disposed (1,3).

**Receipt, Predistribution Shipment, And Distribution**

Procedures must be established and maintained for the receipt, predistribution, and distribution of HCT/Ps. Prior to accepting a HCT/P from another establishment the presence and significance of microorganisms must be evaluated and the product(s) must be inspected for damage and signs of contamination. The inspection process must be based on preestablished specifications that are selected to prevent communicable disease transmission. HCT/Ps must be quarantined until they are verified as having met the specifications (1,3).

The presence of microorganisms can be evaluated using a preprocessing culture prior to processing. Some processors irradiate the HCT/P prior to processing to reduce the bioburden. It may not be possible to evaluate all products for the presence of microorganism prior to transplant, such as corneas (1,3).

At times it may be necessary to transport HCT/Ps between establishments prior to the verification that the product has met all release criteria. This process is predistribution and requires that the HCT/P be kept in quarantine during transport, receipt, and storage until the HCT/P has met release criteria (1,3).

Prior to releasing a HCT/P for distribution the manufacturing records and tracking records must be reviewed. HCT/Ps cannot be distributed that have the following conditions:
- Are in quarantine
- Are determined to be contaminated
- Are from an ineligible donor (or from a donor with an incomplete eligibility determination)
- Otherwise do not meet release criteria designed to prevent communicable disease transmission (1,3).

Documentation must include the following:
- Identification of the HCT/P
- Identification of the sender (i.e., establishment that supplied the HCT/P)
- Activities that were performed on the HCT/P (e.g., inspection, acceptance, or rejection) and the results of the activity
- Date(s) of activities
- Quantity of HCT/P subject to the activity (e.g., received or distributed)
- Disposition of the HCT/P (e.g., identity of the consignee to whom the HCT/P was sent) (1,3).

**Labeling**

Each HCT/P must be clearly labeled with a distinct identification code, description of the type of HCT/P, expiration date, and any applicable warnings. In addition, the HCT/P must be labeled with the name and address of the establishment responsible for the release of the HCT/P, storage conditions, and instructions for use when related to the prevention of the introduction, transmission, or spread of communicable disease (1,3).

**Tracking**

Each HCT/P must be tracked to each manufacturing step performed on that HCT/P, including the tracking of the HCT/P from the donor to the facility receiving the HCT/P. Each step in the handling, processing, testing, shipping, and final disposition must be recorded and traceable. A unique identification code must be assigned and the HCT/P must be labeled with the assigned identification code that will link the HCT/P to the donor and processing records. The assigned identification number cannot link to personal information such as social security number, name, etc. (1,3).

**Audits**

Periodically the establishment is responsible for conducting quality audits to confirm compliance with CGTPs by examining and evaluating objective evidence (1,3).

**Software Verification And Validation**

If software is customized off the shelf and is used for CGTP compliance (e.g., store information to make donor eligibility decisions), the software must be validated. If the computer software is off-the-shelf and has not been customized, the software must be verified and/or validated (1,3).
Complaint Handling

Procedures must be established and maintained for the review, evaluation, and documentation of complaints related to core CGTP requirements and for the investigation of complaints as appropriate (1,3). If a decision is made that an investigation is not required, the rationale supporting that decision must be documented.

Complaint records must include sufficient information to facilitate a review and evaluation of the complaint including the unique identification code assigned to the HCT/P, a description of the complaint (e.g., who, when, what, where), and information regarding the source of the complaint (e.g., contact person, reporting establishment, address, phone/fax/email information) (1,3).

A determination must be made early in the evaluation process as to whether the event is reportable to FDA. The reporting requirements differ for various HCT/Ps. Products regulated under section 351 of the PHS are not subject to the reporting requirements described below (1,3).

Complaints from the consignee or results of communicable disease tests performed by other establishments that recovered HCT/Ps from a shared donor must be included in the complaint handling system (1,3).

Corrective And Preventive Action

An important part of the quality program is the identification of deficiencies, investigation, identification of root cause, risk assessment, assignment of corrective and preventive actions, and verification of effectiveness of those actions taken. All steps in this corrective and preventive action program must be documented (1,3).

Recordkeeping

A record management system must be established and maintained to support the CGTP requirements. Records must be maintained concurrently with each step required in 21 CFR 1271 performed. Records must be accurate, indelible, and legible (1,3). Records must be readily retrievable; therefore, if records are stored at multiple locations there must be a system in place for the timely retrieval of those records. The records for determining donor eligibility are especially important and documents must be obtained directly from the source whenever possible. For example, serology and microbiology reports should be obtained from the laboratory responsible for the testing. Death certificates should be obtained from a state health official, etc. (1,3).

Records must be retained for 10 years after their creation except when stated otherwise in 21 CFR 1271. Records pertaining to a specific HCT/P must be retained for 10 years after its administration or after its distribution, disposition, or expiration whichever is longest (3). Cleaning and sanitation records must be maintained for at least three years (1,3).

Records that must be maintained include agreements describing the assignment of manufacturing steps for processing HCT/Ps. The contracts must provide a detailed description of the specific assignments to the contract facility. Copies of the agreements must be available during an establishment inspection (1,3).

REPORTING OF HCT/P DEVIATIONS

As defined in 21 CFR 1271.350 an establishment must investigate HCT/P deviations related to a distributed product for which the establishment performed a manufacturing step. Deviations to core CGTP requirements are reportable if they occurred in the establishment or in the establishment used as a contract facility (1,3,9).

HCT/P deviations that are related to a deviation from core CGTP must be reported to CBER within 45 days of becoming aware of the deviation using Form 3486 (3,9). Examples of the types of deviations that must be reported include but are not limited to the following:

- When material is used in manufacturing that failed to meet specifications
- When an event occurs during the manufacturing process that may affect the safety, purity, or potency of a product that has been distributed (e.g., processing was performed outside of established parameters)
- When there has been an error during product testing that may affect the safety, purity, or potency of a product that has been distributed (e.g., there was no documentation of the testing performed, the testing was not performed correctly, or not performed as required)
- When there has been a labeling error that may affect the safety, purity, or potency of a product that has been distributed (e.g., information was miss-
ing or incorrect such as product type, lot number, missing expiration date)
• When final product specifications were not met and the product was distributed
• When quality control procedures were not followed and the product was distributed (9).

REPORTING OF ADVERSE EVENTS
Reporting requirements defined in 21 CFR 1271.350 apply to all nonreproductive HCT/Ps that meet the definition for HCT/Ps as described in 21 CFR 1271.10. If the HCT/P does not meet the section 361 requirements, adverse reporting is still required under the applicable regulations for medical devices (21 CFR 803), investigational drugs and biological products (21 CFR 312), post market drugs (21 CFR 314), and post market biological drug products (21 CFR 600). Any adverse reaction that involves a communicable disease related to a HCT/P must be investigated and reported if it is fatal, life-threatening, results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention, including hospitalization. Reporting is required only if the HCT/P has been determined to be eligible and available for distribution and must be reported within 15 calendar days from the date of becoming aware. Follow up reports are also required within 15 calendar days when new information becomes available (1,8).

GLOSSARY
Adverse reaction (for HCT/Ps regulated under section 361): A noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.
Available for distribution: The HCT/P has been determined to meet all release criteria.
Complaint: Any written, oral, or electronic communication about a distributed HCT/P that alleges the following: that the HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P; or any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with CGTP requirements.
Distribution: Any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate.
Establish and maintain: Define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis.
Establishment: A place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps. Establishment includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of HCT/Ps; and facilities that engage in contract manufacturing services for a manufacturer of HCT/Ps.
Manufacture: Any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of cell or tissue donor.
Predistribution: Conveyance or shipment of an HCT/P within an establishment or between establishments before it has met its release criteria (i.e., it is not available for distribution).
Processing: 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.
Quality audit: A documented, independent inspection and review of an establishment’s activities related to core CGTP requirements.
Quality program: An organization’s comprehensive system for manufacturing and tracking HCT/Ps in accordance with 21 CFR Part 1271. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.
Quarantine: Storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation.
Reagents and supplies: All materials that are used during manufacture, not just those coming into direct contact with HCT/Ps. Examples of supplies include: drapes, gauze, cleaning swabs, alcohol pads, and instruments. Examples of reagents include: cleaning agents, saline, dimethyl sulfoxide, anticoagulants, and chemical and antibiotic solutions used in processing.
**Recovery:** Obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

**Validation:** Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled.

**Verification:** Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

**REFERENCES**

1. FDA, CBER, *Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*, January 2009.


3. FDA, 21 CFR 1271, Title 21—Food And Drugs, Chapter I—Subchapter L—Regulations Under Certain Other Acts Administered By The Food And Drug Administration, Part 1271, Human Cells, Tissues, And Cellular And Tissue-Based Products.


**ABOUT THE AUTHOR**

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