Analysis of FDA’s Final 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)

General Comments:
• Many sentences were reordered for clarity, but without changing the intent of the guidance.
• Applicable regulations were added and are indicated in parenthesis.
• Referenced FDA guidance documents include the dates of publication.
• PHS Act is now called FD&C Act
• Internet document links are updated

Specific Changes from the Draft CGTP Guidance
(Note: New language is in bold and deleted language is marked by strikethrough.)

I. INTRODUCTION - Addition of the sentence, “This guidance finalizes the draft guidance of the same title dated January 2009.”

II. BACKGROUND – No changes

III. CGTP REQUIREMENTS (§ 1271.150)

C. How Do I Ensure that Another Establishment with Which I Have a Contract, Agreement or Other Arrangement Complies with CGTP Requirements?

Example 2: You should consider including in your contract, agreement, or other arrangement with an establishment a requirement that the establishment provide you with all Form FDA 483s and EIRs that it receives, and copies of its SOPs, and any revisions and a requirement to be notified of proposed changes to any test kit or testing methodology being used.

Example 3: . . . and that your contractor has a quality program that addresses the SOPs and records generated for these processing steps applicable to core CGTPs, including 21 CFR 1271.220 (§ 1271.160(a)).

Example 5: You should also request review copies of applicable storage SOPs to ensure that your distributed HCT/Ps are held stored according to your specifications.

E. Do I Have to Follow CGTP Requirements if My HCT/Ps Are Not 361 HCT/Ps Also Regulated as a Biological Product, Drug, or Device?

This section is reworded and the paragraphs are reordered. New wording is below:

In many instances, the CGMP regulations and CGTP regulations require the same manufacturing practice, and compliance with the CGMP regulations results in compliance with the applicable CGTP requirements.
However, for the following CGTP requirements, the CGTP requirement would require additional manufacturing practices, because the CGTP requirements would not be partly or completely covered by a corresponding CGMP regulation requiring the same practice:

- certain parts of manufacturing arrangements under a contract, agreement, or other arrangements (§ 1271.150(c)(1)(ii) and (iii));
- certain records for contracts and agreements (§ 1271.270(e));

The section on HCT/Ps regulated as medical devices is similarly reworded.

IV. EXEMPTIONS AND ALTERNATIVES (§ 1271.155)

B. Where Do I Send a Request for an Exemption or Alternative? A new internet link is provided.

C. Can an Exemption or Alternative Apply to More Than One Establishment?
A new paragraph was added:

An HCT/P that is the subject of an exemption or alternative request may be distributed to another establishment for utilization. The HCT/P must be distributed with the accompanying records required under § 1271.155(f) (i.e., documentation of the grant of the exemption or alternative and the date on which you began operating under the terms of the exemption or alternative).

V. ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM (§ 271.160)

D. What Must I Do When Information is Received From Sources Outside the Establishment, and What Must I Do with this Information?

Deleted the following from the third bullet - We recommend that recalls be reported to the FDA district office’s recall coordinator.

E. With Whom Must an Establishment Share Information Pertaining to the Possible Contamination of or Potential for Transmission of Communicable Disease by an HCT/P?

Added the following sentence (previously part of Example 2):

We recommend that these procedures be defined in your contracts, agreements, and other arrangements with other establishments.

Example 1: Added the applicable regulations (§ 1271.160(b)(2)(i)) and (§ 1271.160(b)(2)(iii)).

G. What Must the Quality Program Ensure Regarding Personnel?

The FDA expanded on the training of personnel in specific positions by adding 3 bullets:
The quality program must ensure that personnel involved in activities related to core CGTP requirements have proper training and education and experience to perform those activities, and that personnel perform only those activities for which they are qualified and authorized (see §§ 1271.170 and 1271.160(b)(4)).

- personnel performing recoveries are certified by a professional organization;
- individuals under contract, agreement, or other arrangement with your establishment that engage solely in recovering cells or tissues, who are exempt from registration but not from other applicable requirements (§ 1271.15(f)), have proper training, education and/or experience as applicable to the recovery activities they perform;
- donor eligibility determinations are performed by a responsible person who has the professional training to recognize risk factors for and clinical evidence of communicable disease agents by review of symptoms, signs and clinical laboratory results; and
- personnel performing investigations of complaints or adverse reactions related to a possible communicable disease have the training and experience to review and interpret clinical records, including pathology reports, laboratory results and medical/surgical interventions.

I. When HCT/P Deviations Occur, What is the Role of the Quality Program?

Provided a more specific example of an HCT/P deviation:

Example: HCT/Ps are recovered, and the donor is determined to be eligible based on results of donor screening and testing. However, a later review of donor records determines that the donor was incorrectly determined to be eligible because the donor was not free from clinical evidence of infection due to relevant communicable disease agent or disease, as specified in your establishment’s SOPs.

L. If the Establishment Relies on Computer Software to Comply with Core CGTP Requirements, What Activities Must be Performed Before Implementing the Software?

You must approve and document these activities and results before implementation (§ 1271.160(d)).

VI. PERSONNEL (§ 1271.170)

New wording is in bold:

An individual under contract agreement or other arrangement to a registered recovery establishment who performs only these functions and no other manufacturing steps does not have to register independently (§ 1271.15(f)).

- setting up a program for demonstration of competency for their assigned functions when observed by a supervisor or appropriately experienced designee.

VII. PROCEDURES (§ 1271.180)

B. Do Procedures Have to be Physically Maintained in the Area Where the Operation is Performed?

New sentence added:
As long as a paper and/or electronic copy of the SOPs is physically available, additional methods of obtaining information, such as an immediate communication method using wired or wireless technologies from personnel with questions to personnel who have access to current procedures, could be used to resolve, answer or clarify questions that arise during operations.

VIII. FACILITIES (§ 1271.190)

B. What Facility Cleaning and Sanitation Issues Must I Consider?

Example: You use a broad-spectrum disinfectant that has been demonstrated to inactivate bacteria and fungi on surfaces. You should follow the manufacturer's instructions for proper dilution and adequate contact time and document that all parameters were met have been achieved during each cleaning.

F. How Do Facility-Related Requirements Apply to Recovery of HCT/Ps?

You should consider the following elements issues when evaluating an area used for recovery:

- Is there access to running water and a sink;

*Before entering into a contract with a recovery establishment, a processor could examine the facilities where recoveries take place.*

IX. ENVIRONMENTAL CONTROL AND MONITORING (§ 1271.195)

E. How Often Should I Perform Environmental Monitoring?

- personnel monitoring (e.g., gloves touch plates).

X. EQUIPMENT (§ 1271.200)

A. What Are the General Equipment Requirements?

Equipment used in the manufacture of HCT/Ps must be of appropriate design for its use and must be suitably located and installed to facilitate operations including cleaning and maintenance.

B. Do I Have to Qualify or Certify Equipment (Installation Qualification, Operational Qualification, Performance Qualification)?

*Environmental monitoring is often periodically performed between certifications.* An event or activity that warrants recertification of the laminar flow hood would include, but is not limited to, repair or replacement of parts.

I. What Records Related to Equipment Must I Keep?

You should keep records for cleaning and maintenance of equipment (including simple instruments that are regularly washed and disinfected), tools, and other equipment used or reused in the manufacturing of HCT/Ps to document that the items were adequately cleaned and maintained in order to prevent their contamination or cross-contamination by communicable disease agents (1271.200(e)).
Deleted the following sentence which was redundant and mentioned previously:

*Under § 1271.200(e), you must display records of recent maintenance, cleaning, sanitizing, calibration, and other activities on or near each piece of equipment, or make the records readily available to the individuals responsible for performing these activities and to the personnel using the equipment.*

**XI. SUPPLIES AND REAGENTS (§ 1271.210)**

**B. What Verification is Required for Supplies and Reagents?**

*For supplies such as sterile drapes or gloves that are not expected to have a COA, we recommend that you obtain information from the vendor on the relevant specifications and the manufacturing process of the supply, including any sterilization process.*

**C. What Are Some Methods to Verify Reagents or Supplies?**

*You should verify that shipping containers used to transport HCT/Ps from the recovery site to storage or to the processor, and/or to transport HCT/Ps from storage to the processor are capable of maintaining the expected storage environment relative to controlling contamination.*

**XII. RECOVERY (§ 1271.215)**

**C. What Are Ways in Which a Recovery Establishment Could Identify the Donor Prior to HCT/P Recovery?**

*For deceased donors, you could reproduce the donor's identification tag or band by photographing it, thereby documenting its content, or manually reproduce the contents of the identification method using a standardized form.*

**D. What Are Ways in Which a Processor Receiving HCT/Ps From a Recovery Establishment Under Contract with the Processor Could Verify the Identity of the Donor and Could Ensure That the Donor Records Are From the Same Donor as the HCT/Ps?**

*Before entering into a contract with a recovery establishment, a processor could examine the facilities where recoveries take place.*

**XIII. PROCESSING AND PROCESS CONTROLS (§ 1271.220)**

**A. What is Processing?**

*Example 1: Corneal processing could include separation of the corneoscleral rim from the globe following enucleation (removal of the eye), cutting of corneas in preparation for Endothelial Keratoplasty (EK) procedures, microbiological culture of the rim, and placement of the cornea in a vial containing storage/transport media. If the cornea is recovered in situ and placed directly in the storage media with no further preparation, we would not consider that processing.*

*Example 2: Processing of hematopoietic stem/progenitor cells recovered by apheresis cell products could include red cell or plasma removal, cell selection, and cryopreservation for long-term storage.*
Example 3: Heart valve processing could include dissection and shaping of the aortic and pulmonic valves, antibiotic treatment, and cryopreservation.

C. What in-Process Control and Testing Must I Perform?

This may not be the case if a small portion of the large musculoskeletal HCT/P or companion HCT/P (i.e., HCT/Ps adjacent to the HCT/P that is processed along with the HCT/P) is cultured. In a March 15, 2002, Morbidity and Mortality Weekly Report, the Centers for Disease Control and Prevention (CDC) recommended that you consider performing both destructive and swab cultures of musculoskeletal HCT/Ps (Ref. 11).

D. Why Are Pre-Processing (Microbiological) Cultures Important?

Section 1271.220(c) requires in-process control and testing. We believe that pre-processing cultures (sometimes referred to as pre-disinfection cultures) for musculoskeletal HCT/Ps (e.g., bone, tendon, ligament) should be performed because they are a critical in-process control. We further recommend that all results for pre-processing cultures from a particular donor should be considered when determining whether to accept or reject incoming musculoskeletal HCT/Ps from that donor prior to processing. Based on our Tissue Safety Team’s investigations of adverse reaction reports related to transmission of communicable disease by musculoskeletal HCT/Ps, we recommend processors properly assess and utilize the results of pre-processing cultures.

... Thus, if musculoskeletal HCT/Ps are processed with bioburden in excess of the level that the process has been validated to remove or inactivate (e.g., multiple pre-processing cultures from a single donor are positive for enteric or pathogenic microorganisms, or are positive for microorganisms that have proved most difficult to reduce or eliminate, such as Clostridium or Streptococcus pyogenes (group A strep)), there is no assurance that the process will result in the reduction or removal of bioburden to acceptable limits or reduce the risk of transmission of communicable disease.

We recommend that for all HCT/Ps, you:

- Carefully consider the capability of your microbiological testing, disinfection, and sterilization processes when you evaluate pre-processing cultures to determine whether or not the HCT/Ps should be processed.

We further recommend that for musculoskeletal HCT/Ps, you:

- **Discard all** Do not process any musculoskeletal HCT/Ps from a donor that has any musculoskeletal pre-processing cultures positive for Clostridium, Streptococcus pyogenes (group A strep), or any other microorganisms that you have determined to be difficult to eliminate, unless you have a terminal sterilization process validated to a sterility assurance level (SAL) of 10-6.

- **Discard all** Do not process any musculoskeletal HCT/Ps from a donor who has multiple musculoskeletal pre-processing cultures positive for enteric or pathogenic microorganisms, unless you have a terminal sterilization process validated to a SAL of 10-6.
F. What Special Processing and Process-Control Considerations Must I Have for Dura Mater?

Therefore, § 1271.220(d) requires use of a validated process when one is published subject to the exception noted above and below.

To assist you in identifying newly published, validated processes, we intend, pursuant to good guidance practices set out in 21 CFR 10.115, to advise you when we have identified the existence of a published, validated process that reduces the risk of TSE, and we would ordinarily solicit public comment before issuing a final guidance.

You can find additional information about processing and process controls for dura mater in FDA’s “Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Human Dura Mater”.

XIV. PROCESS CHANGES (§ 1271.225)

However, under § 1271.230(c), when changes to a validated process subject to § 1271.230(a) occur, you must review and evaluate the process and perform revalidation where appropriate (see section XV.F. of this guidance).

XV. PROCESS VALIDATION (§ 1271.230)

C. How Do I Perform a Validation Study?

The FDA guidance entitled, “Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation” dated March 2002 (Ref. 12), provides information about validation. The recommendations in the FDA guidance entitled, “Guidance for Industry: Process Validation: General Principles and Practices” dated January 2011 (Ref. 9), also may be useful to consider. Another useful reference is “Guideline on General Principles of Process Validation” (Ref. 9).

XVI. LABELING CONTROLS (§ 1271.250)

There are no changes from the draft guidance language.

XVII. STORAGE (§ 1271.260)

E. What Temperature Limits Must I Establish During Manufacturing?

Example: If you determine that your HCT/P can be stored at ambient room temperatures, you must define the temperature limits (e.g., 20-25 degrees centigrade), and document and maintain records of environmental control and monitoring activities (§§ 1271.260(e) and 1271.195(a)). These records must be reviewed periodically to ensure that the temperatures have been within acceptable limits (§ 1271.260(e)).

XVIII. RECEIPT, PRE-DISTRIBUTION SHIPMENT, AND DISTRIBUTION OF AN HCT/P (§ 1271.265)

A. What Should I Do Before Accepting an HCT/P From Another Establishment?

When you receive an HCT/P, you should visually inspect the shipping container, packaging, HCT/P container, and HCT/P for damage and contamination. If there are indications that contamination or
cross-contamination of the HCT/P could have occurred, you should quarantine the HCT/P until your investigation is complete.

**B. What Are Ways That I Can Evaluate an Incoming HCT/P for Microorganisms and Inspect for Damage and Contamination? Am I required to perform a microbiological culture of an HCT/P prior to processing the HCT/P?**

(Previously this was under section A)

*When you receive an HCT/P, you should visually inspect the shipping container, packaging, HCT/P container, and HCT/P for damage and contamination. If there are indications that contamination or cross-contamination of the HCT/P could have occurred, you should quarantine the HCT/P until your investigation is complete.*

*Under § 1271.265(a), you must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. One way to accomplish this another method used to evaluate an HCT/P for contamination is to culture the HCT/P prior to processing. This culture is known as the pre-processing culture (sometimes referred to as the pre-disinfection culture). Recovery establishments may perform the culture and send the results to the processor. Alternatively, using pre-established criteria, the processor may perform the culture and based upon the results determine whether to reject or accept the HCT/P for processing. For instance, some processors may irradiate the HCT/P to reduce the bioburden prior to additional processing, depending upon the amount and/or type of microorganisms detected.*

It may not be possible to culture some HCT/Ps prior to processing. For instance, corneas are recovered and then placed immediately into transport media that contains antibiotics. While corneas recovered *in situ* are not processed, they are received at the eye bank already packaged in a container with transport media. *Ideally, we recommend that a corneoscleral rim culture should be taken at the time of recovery, unless otherwise justified.* If the container in which the cornea is placed after recovery is not fully intact when received by the eye bank, one should assume the possibility of contamination and presence of microorganisms. For storage/transport solutions containing a pH indicator, a color change could indicate contamination.

**G. May I Release an HCT/P if it Has Been Manufactured Under a Departure From a Procedure?**

*Example 1: You arrive at a recovery site to recover HCT/Ps from a deceased donor and you discover that the cleaning solution that you routinely use to disinfect the work surface is not available. You clean the surface with an alternative cleaning solution and proceed to recover HCT/Ps. The HCT/Ps are sent to a processing establishment. The HCT/Ps must not be made available for distribution until a responsible person determines that the alternate cleaning solution is as effective as the routine cleaning solution and does not increase the risk of HCT/P contamination (see § 1271.265(c)(3)).*

*Example 2: You are processing a hematopoietic stem cell product in the LFH. While engaged in aseptic processes you realize that the reagent you placed in the hood is a new in-house reagent that meets specifications designed to prevent transmission of communicable disease, but your establishment's SOP has not yet been updated to reflect the acceptance of the new reagent. The reagent specified in the SOP is not immediately available in your laboratory. You complete the aseptic processing using the new reagent and then immediately document the departure from procedure. The cell product must*
not be made available for distribution until a responsible person determines that use of the new reagent does not increase the risk of contamination of the product (§ 1271.265(c)(3)).

J. Am I Required to Determine the Appropriate Shipping Conditions?
No changes to previous verbiage.

M. Am I Permitted to accept HCT/Ps that are returned to me and Place the Returned HCT/Ps Back Into Inventory?

If return is permitted, you should specify the conditions under which the return could be accepted returned to inventory.

XIX. RECORDS (§ 1271.270)

B. What Kind of Records Management System Must I Have?

Example: A recovery establishment under contract with a processor sends HCT/Ps to the processor. The recovery establishment should send all relevant records, including donor records and cleaning records relating to recovery site suitability as described in section XII.B., to the processor. The recovery establishment must maintain copies of all transferred records and organize them in its records management system.

C. What Are Acceptable Methods of Record Retention?

Example: You are a processor that receives paper records of the donor’s medical history from the recovery establishment. You review the medical history as part of the donor eligibility determination. At a later time, you scan the paper records and save them as a .pdf file on a computer that is backed up. The electronic records are true copies of the paper records. Therefore, you may destroy the paper records. However, if instead of scanning, you were to re-type (transfer) the information into the computer, you would be creating a new record, not making a true copy. Then we cannot be certain that this is a “true copy” or if errors have been made while re-typing, either intentionally or unintentionally. So in this scenario, you would be required to keep the original paper (hardcopy) records as proof of concurrent recordkeeping (§ 1271.270(a)).

D. For How Long Must I Retain my HCT/P Manufacturing Records?

Example 2: A cord blood establishment goes out of business, and transfers the remaining products in inventory to one or more different cord blood establishments. All of the original manufacturing records or complete copies for these products should be transferred to the establishment(s) receiving the cord blood and kept. The receiving establishment(s) will be responsible for maintaining those records in such a way as to facilitate review of an HCT/P’s history before making it available for distribution and, if necessary, subsequent to the HCT/P’s release as part of a follow up evaluation or investigation (§ 1271.270(b)). The receiving establishment(s) must maintain the manufacturing records for at least 10 years after the date the HCT/P is administered (§ 1271.270(d)).

XX. TRACKING (§ 1271.290)
A. How Extensive a Tracking System Must I Establish and Maintain?

Alternatively, if you are an establishment that performs some but not all of the steps in the manufacture of an HCT/P in which you handle the HCT/P, you may participate in a system of HCT/P tracking established and maintained by another establishment responsible for other steps in the manufacture of the same HCT/P, provided that the tracking system complies with all § 1271.290 requirements (§ 1271.290(b)(2)). You should verify that the tracking system is effective, especially if you participate in a tracking system maintained by another establishment responsible for other steps in the manufacture of the same HCT/P. Each establishment has the flexibility to define the tracking system and ensure that the establishment meets the requirements for tracking.

B. Must Each HCT/P Have a Distinct Identification Code?

Under § 1271.290(c), each HCT/P that you manufacture must be assigned and labeled with a distinct identification code that relates the HCT/P to the donor and to all records pertaining to the HCT/P. The code must be created specifically for tracking purposes and may not include any protected health information, such as the donor’s name, social security number or medical record number (with some exceptions as noted below).

C. How Do I Ensure Tracking of HCT/Ps Distributed From My Establishment to Consignees or for Final Disposition?

Under § 1271.290(d) and (e), as part of your tracking system, you must establish and maintain a method for recording the distinct identification code and type of each HCT/P distributed to a consignee to enable tracking from the consignee to the donor (§ 1271.290(d)).

As part of the tracking system requirements, you could also supply self-addressed envelopes, or an email or web address to return the disposition information for your tracking system. Regular reminders could be sent to hospitals or other consignees (e.g., surgical centers, dental offices) when disposition information is not received.

D. Are There Specific Requirements for Dura Mater Donors?

Examples of appropriate specimens are serum or lymph nodes. We also recommend that you archive frozen and fixed samples of both donor brain and dura mater HCT/Ps. The donor brain samples should include at least 5 grams of the frontotemporal region. We recommend in “Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Human Dura Mater” (Ref. 8), that you retain these specimens for 10 years based on the current scientific knowledge regarding the development of screening tests and expectation that, as the science evolves, screening tests could become available. Examples of these specimens are serum or lymph nodes. We also recommend that you archive frozen and fixed samples of both donor brain and dura mater HCT/Ps. The donor brain samples should include at least 5 grams of the frontotemporal region. You must retain records for archived specimens of dura mater for 10 years after the appropriate disposition of the specimens (§ 1271.270(d)).
XXI. COMPLAINT FILE (§ 1271.320)

A. What Information About Each Complaint Must I Have in My Complaint File?

When copying complaint files, we will take steps to protect the identity of the donor and/or recipient. We are required to maintain the confidentiality of the records/files and protect the information from inappropriate release under the Standards for Privacy of Individually Identifiable Health Information (67 FR 53181, August 14, 2002) and other applicable laws and regulations.

B. How Should I Review and Evaluate Complaints?

Under § 1271.320(c), you must review and evaluate each complaint relating to core CGTP requirements to determine if the complaint is related to an HCT/P deviation or to an adverse reaction and to determine if a report under § 1271.350 or other applicable regulation is required.

XXII. REPORTING (§ 1271.350)

A. What Are the General Requirements for Adverse Reaction Reports?

Adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response (§ 1271.3(y)). We recognize that there may be situations in which there are multiple possible causes of a patient’s problem. Nevertheless, if one of the reasonable possibilities is that the HCT/P caused the problem, then this would meet the definition of “adverse reaction.” This would include situations in which the relationship between the response and the HCT/P is “unlikely” but nevertheless possible.

Example 2: A patient develops endophthalmitis after receiving a cornea allograft. A posterior chamber culture grows Staphylococcus epidermidis. Although the eye bank did not culture the cornea prior to release, the surgeon performed a pre-implant culture, which was negative. The surgeon ordered additional antibiotics to treat the endophthalmitis. You must report this adverse reaction, even though the pre-implant culture was negative, because there is a reasonable possibility that the cornea caused this response, the adverse reaction involves a communicable disease, and it necessitated medical intervention.

B. What is Considered a Medical or Surgical Intervention That I Must Report to FDA?

Example 2. Medical intervention would include re-hospitalizing a patient who was discharged following surgery for treatment of a known or suspected infection, or its consequences, which are known or suspected to be related to the HCT/P.

C. How Do I Report Adverse Reactions to FDA?


G. How Do I Report an HCT/P Deviation to FDA?

Updated links: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM061463.pdf
XXIII. LABELING (§ 1271.370)

A. What Information Must Appear on the HCT/P Label?

Under § 1271.370(a), you must label each HCT/P made available for distribution clearly and accurately. Note that a label can include the affixed container label or an attached tie-tag. You must place the following information on the HCT/P label (§ 1271.370(b)):

- distinct identification code affixed to the HCT/P container, and assigned in accordance with § 1271.290(c) (§ 1271.370(b)(1));
- description of the type of HCT/P (§ 1271.370(b)(2));
- expiration date, if any (§ 1271.370(b)(3)); and
- warnings required under §§ 1271.60(d)(2), 1271.65(b)(2), or 1271.90(b), if applicable and physically possible. If it is not physically possible to include these warnings on the label, the warnings must accompany the HCT/P (§ 1271.370(b)(4)). Note that the label can include the affixed container label or an attached tie-tag.

XXIV. REFERENCES

Includes all updated links to documents and one new reference.