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)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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I. INTRODUCTION

We, FDA, are issuing this guidance to provide you, establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps), with recommendations for complying with Current Good Tissue Practice (CGTP) requirements under Title 21 Code of Federal Regulations, part 1271, subpart D (21 CFR part 1271, subpart D)[1], and requirements under 21 CFR part 1271, subpart E (Additional requirements for establishments described in § 1271.10). This guidance also addresses whether the establishment registration and HCT/P listing requirements under 21 CFR part 1271, subparts A and B apply in certain instances.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. What is the scope of this guidance?

This guidance provides recommendations for complying with the requirements under 21 CFR part 1271, subparts D and E during manufacture of HCT/Ps. However, at this

[1] The requirements of 21 CFR part 1271, subpart C (Donor Eligibility) are a component of CGTP requirements (21 CFR 1271.45(a)), however this guidance does not directly address 21 CFR part 1271, subpart C requirements.

time subpart D (with the exception of § 1271.150(c) and § 1271.155) and subpart E do not apply to reproductive HCT/P establishments regulated solely under section 361 of the Public Health Service (PHS Act).

This guidance applies to establishments that manufacture HCT/Ps that meet the criteria listed in § 1271.10 and are regulated solely under section 361 of the PHS Act and the regulations in 21 CFR part 1271.[2] CGTP requirements also apply to HCT/Ps regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act (the Act) (see § 1271.1(b)(2)). This guidance also addresses whether the establishment registration and HCT/P listing requirements under part 1271, subparts A and B apply in certain instances.

For additional information on subparts C and E refer to the following guidances: "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 1); and "Guidance for Industry, MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 2).

B. Who should read this guidance?

This guidance is intended for any HCT/P establishment that performs a manufacturing step and is responsible for complying with CGTP requirements. Establishment, as defined under § 1271.3(b)(1), means 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.

Establishments may engage another establishment under a contract, agreement, or other arrangement to perform any manufacturing step. Such allocations of responsibility must comply with § 1271.150(c), and the other establishments must also comply with the requirements applicable to the manufacturing steps they perform.

In this guidance, "you" means:

- the establishment that performs a manufacturing step; or
- the establishment that performs a manufacturing step under contract, agreement or other arrangement for another HCT/P establishment.

[2] An HCT/P that falls into this category is referred to as a "361 HCT/P".

III. CGTP REQUIREMENTS (§ 1271.150)

CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps in a way that prevents the introduction, transmission, or spread of communicable diseases by HCT/Ps (§ 1271.150(a)).[3] Manufacture, as defined in § 1271.3(e), means, but is not limited to, 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. Under § 1271.145, you must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases. Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents (§ 1271.150(a)).

A. What are core CGTP requirements?

Core CGTP requirements (§ 1271.150(b)) are those requirements that directly relate to preventing the introduction, transmission, or spread of communicable disease by HCT/Ps. The core CGTP requirements include requirements for:

- facilities (§ 1271.190(a) and (b));
- environmental control (§ 1271.195(a));
- equipment (§ 1271.200(a));
- supplies and reagents (§1271.210(a) and (b));
- recovery (§ 1271.215);
- processing and process controls (§ 1271.220);
- labeling controls (§ 1271.250(a) and (b));
- storage (§1271.260(a) through (d));
- receipt, predistribution shipment, and distribution of an HCT/P (§ 1271.265(a) through (d)); and
- donor eligibility determinations, donor screening, and donor testing (§§ 1271.50, 1271.75, 1271.80, and 1271.85).

Other CGTP requirements discussed in this guidance support the core CGTP requirements (e.g., the required records management system in § 1271.270(b)). Although we have identified core CGTP requirements, you must follow all CGTP requirements (§ 1271.150(a)). If you perform only some manufacturing operations, see § 1271.150((c)(1)(i) and section III.B. of this document.

[3] The CGTP provisions specifically governing determinations of donor eligibility, including donor screening and testing, are set out separately in 21 CFR part 1271, subpart C (§ 1271.45(a)).

B. What requirements must I follow if I perform only some manufacturing operations?

Under § 1271.150(c)(1)(i) you must comply with those requirements applicable to the operations that you perform. If you engage another establishment under a contract, agreement, or other arrangement to perform any step in manufacture for you, that establishment must comply with requirements applicable to that manufacturing step (§ 1271.150(c)(1)(ii)). Examples of establishments performing steps in manufacturing would be a laboratory performing communicable disease testing, or an irradiation facility performing terminal sterilization of an HCT/P.

C. How do I ensure that another establishment with which I have a contract, agreement or other arrangement complies with CGTP requirements?

Under § 1271.150(c)(1)(iii), before entering into a contract, agreement, or other arrangement with another establishment to perform any step in manufacture for you, you must ensure that the establishment complies with applicable CGTP requirements.[4]

Some ways that you could ensure the other establishment's compliance with applicable CGTP requirements include the following:

- ensure that responsibilities are listed and understood as they relate to CGTP requirements;
- review test kit package inserts that are used by a contract test laboratory;
- review standard operating procedures (SOPs) applicable to CGTP requirements;
- review certifications (e.g., Clinical Laboratory Improvement Act (CLIA), certificate of analysis), where appropriate;
- review previous compliance actions such as FDA Forms 483 and Establishment Inspection Reports (EIRs);
- perform for-cause and random comparisons of documentation provided by your contractor with source documents from the originator of the material;
- ensure that the establishment has a quality program that addresses the operations that they perform for you; and/or
- perform periodic audits of the establishment. We recommend that such an audit include a review of compliance with all 21 CFR part 1271 requirements applicable to the operations that the establishment performs for you.

Example 1. You are a processor that receives HCT/Ps from a recovery firm under contract with you. You have decided to audit the recovery firm annually to ensure compliance with CGTP requirements for recovery, donor medical history interview, obtaining specimens for communicable disease testing, and shipping HCT/Ps to you at

[4] We interpret the regulation as saying that entering into a contract, agreement, or other arrangement means the execution or ratification, and not the negotiation, of the contract, agreement, or other arrangement.

appropriate temperatures. During the audit you should consider reviewing some of the records that were previously provided by the recovery establishment to confirm their accuracy by checking with the source of the information for a representative number of these records (e.g., directly contacting the attending physician, the communicable disease testing laboratory, the coroner, the hospital or the next of kin). You also may want to accompany the recovery team on a recovery to review adherence to procedures and review the quality program activities.

Example 2: You should ensure that your contract laboratories that perform HCT/P donor testing have the appropriate CLIA certification and ensure that they are using the appropriate FDA-licensed, approved, or cleared donor screening tests according to the manufacturer's instructions (e.g., by reviewing a listing of the tests, manufacturer and copies of the test kit package insert). Such laboratories are considered establishments (§ 1271.3(b)) that manufacture (§ 1271.3(e)) HCT/Ps and are required to register with FDA (§ 1271.21). You should review their most recent validated Form FDA 3356 for registration and listing to ensure that they are in compliance with § 1271.10(b). They must also have a quality program appropriate for the operations they perform (§ 1271.160(a)). You should consider including in your contract, agreement, or other arrangement with the establishment a requirement that the establishment provide you with all FDA Form 483s and EIRs that they receive, and copies of their SOPs and any revisions. After your initial assessment to ensure that the establishment performing the manufacturing step for you is in compliance, you should check with them periodically to ensure their continued operational compliance.

Example 3: You contract out some of your processing steps such as terminal sterilization and microbial testing. You should have assurance that your contractor's processing steps have been verified or validated to be in compliance with all of the requirements in §§ 1271.220, 1271.225, and 1271.230, and that your contractor has a quality program that addresses the SOPs and records generated for these processing steps (§ 1271.160(a)).

Example 4: You are the establishment that determines that an HCT/P meets all release criteria and you make the HCT/P available for distribution. Whether or not you are the actual distributor, you are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with part 1271, subparts C and D, and any other applicable requirement (§ 1271.150(c)(2)).

Example 5: You contract out the actual distribution of your product. You should ensure that distribution records are kept so that HCT/Ps can be tracked back to you if you are the establishment that makes the HCT/P available for distribution (see § 1271.150(c)(2)). You should also request copies of applicable storage SOPs to ensure that your distributed HCT/Ps are held according to your specifications.

D. What steps should I take if I become aware and then determine that the establishment performing any step in manufacture for me is no longer in compliance with 21 CFR part 1271?

Under § 1271.150(c)(1)(iii), if you become aware that the establishment may no longer be in compliance with applicable CGTP requirements, you must take reasonable steps to ensure the establishment complies with those requirements. These steps may include reviewing the establishment's corrective action plan and verifying that corrective actions have been taken under the establishment's quality program. If you have taken reasonable steps to ensure the establishment is in compliance, but you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement, or other arrangement with the establishment (§ 1271.150(c)(1)(iii)).

E. Do I have to follow CGTP requirements if my HCT/Ps are not 361 HCT/Ps?

Yes, CGTP requirements as well as drug current good manufacturing practice (CGMP) requirements or device quality system (QS) regulation requirements apply. The current CGMP regulations in 21 CFR parts 210 and 211 or the QS regulation in part 820 apply to an HCT/P depending upon whether the product is regulated as a drug, device or biological product (§ 1271.150(d)) (see especially, §§ 210.1(c), 210.2, 211.1, and 820.1). These CGMP and QS regulations supplement the CGTP requirements, and in the event that a regulation in 21 CFR part 1271 is in conflict with a requirement in 21 CFR parts 210, 211, or 820, the regulations more specifically applicable to the product in question will supersede the more general.

1. For HCT/Ps regulated as biological products – Current Good Tissue Practice and Current Good Manufacturing Practice

HCT/Ps regulated as biological products are regulated under sections 351 and 361 of the PHS Act and the Act. These HCT/Ps include some hematopoietic progenitor cells (HPC) and other cellular products (e.g., allogeneic pancreatic islet cells, cell-based cancer vaccines and immunotherapies, chondrocytes). CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps.

The CGMP requirements in 21 CFR parts 210 and 211 govern the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to ensure that such drug meets the requirements of the Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. These CGMP requirements apply to biological products, regulated under section 351 of the PHS Act, that meet the definition of drug in the Act. Due to the broader scope of these regulations, most of the CGMP regulations under 21 CFR parts 210 and 211 would apply to HCT/Ps regulated as biological products. Additionally, for the

most part, CGTP requirements would be covered under the broader CGMP regulations. Compliance with these CGMP regulations would result in compliance with applicable CGTP requirements.

If your HCT/P is regulated as a biological product, you must follow the listed CGTP requirements because they would not be partly or completely covered by a corresponding CGMP requirement:[5]

- all donor eligibility requirements (part 1271, subpart C);
- prevention of the introduction, transmission, or spread of communicable diseases (§ 1271.145);
- certain parts of manufacturing arrangements--contracts and other arrangements (§§ 1271.150(c)(1)(ii) and (iii));
- procedures for sharing with other establishments information pertaining to possible contamination or potential for transmission of communicable disease (§ 1271.160(b)(2));
- audits (§ 1271.160(c));
- prohibition on pooling (§ 1271.220(b));
- predistribution shipment (§ 1271.265(b));
- HCT/P availability for distribution only after donor eligibility established (§ 1271.265(c)(2));
- packaging and shipping requirements (§ 1271.265(d));
- record-keeping for 10 years (§ 1271.270(d)) (but facility cleaning and sanitation records for 3 years (§ 1271.190(d)(2));
- certain records for contracts and agreements (§ 1271.270(e)); and
- tracking (§ 1271.290(a) through (g)).

An example in which a corresponding CGMP requirement partially covers a CGTP requirement is the quality program requirement (§ 1271.160). Some quality program requirements are covered by specific subparts and sections of part 211 such as § 211.22 (quality control unit), part 211, subpart F (production and process controls), § 211.160(a) (specifications and standards, sampling plans, and test procedures, reviewed and approved by the quality control unit), § 211.192 (production record review), and § 211.198 (complaint files). If you manufacture HCT/Ps regulated as biological products you must follow these part 211 requirements, as well as certain requirements found under § 1271.160.

An example in which a CGTP requirement is not covered by a CGMP requirement is the CGTP requirement for predistribution shipment in § 1271.265(b). Under § 1271.265(b), if you ship an HCT/P within your establishment or between establishments (e.g., shipment from a procurer to a processor), and the HCT/P is not available for distribution as described in

[5] Exemptions and alternatives to any requirement in part 1271, subpart C or D are applicable (§ 1271.155).

§ 1271.265(c), then you must first determine and document whether pre-established criteria designed to prevent communicable disease transmission have been met, and you must ship the HCT/P in quarantine.

2. For HCT/Ps regulated as medical devices

HCT/Ps regulated as medical devices are regulated under section 361 of the PHS Act and the Act. CGTP requirements and the QS regulation in part 820 are applicable.

An example of an HCT/P regulated as a medical device is demineralized bone combined with a handling agent. Due to the broader scope of the medical device regulations, most of the QS regulation would be applicable for HCT/Ps that are not regulated solely under section 361 of the PHS Act and meet the definition of devices in the Act. If your HCT/P is regulated as a medical device, you must follow the listed CGTP requirements because they would not be partly or completely covered by sections of the QS regulation: [6]

- all donor eligibility requirements (part 1271, subpart C);
- prevention of the introduction, transmission, or spread of communicable diseases (§ 1271.145);
- certain parts of manufacturing arrangements--contracts and other arrangements (§§ 1271.150(c)(1)(ii) and (iii));
- procedures for sharing with other establishments information pertaining to possible contamination or potential for transmission of communicable disease (§ 1271.160(b)(2));
- prohibition on pooling (§ 1271.220(b));
- predistribution shipment (§ 1271.265 (b));
- HCT/P availability for distribution only after donor eligibility established (§ 1271.265(c)(2));
- packaging and shipping requirements (§ 1271.265(d));
- record-keeping for 10 years (§ 1271.270(d)) (but facility cleaning and sanitation records for 3 years (§ 1271.190(d)(2));
- certain records for contracts and agreements (§ 1271.270(e)); and
- tracking (§ 1271.290(a) through (g)).

An example in which the corresponding sections of the QS regulation completely cover the CGTP requirements are the requirements for acceptance activities and nonconforming products. Therefore, if you manufacture HCT/Ps regulated as medical devices and comply with §§ 820.50, 820.80, 820.86, and 820.90, then you would be in compliance with the CGTP requirements.

[6] Exemptions and alternatives to any requirement in part 1271, subpart C or D are applicable (§ 1271.155).

An example in which the corresponding section of the QS regulation partially covers a CGTP requirement are the requirements for a quality program. Quality program requirements in 21 CFR part 1271 that are partially covered by specific sections of 21 CFR part 820 include § 820.5 (Quality System), § 820.20(a through e) (Management Responsibility), § 820.22 (Quality Audit), § 820.70 (Production and Process Controls), and § 820.100 (Corrective and Preventive Action). Specific sections of 21 CFR part 1271 not covered by the requirements in 21 CFR part 820 include § 1271.160(b)(1) and (b)(2). If you manufacture HCT/Ps regulated as medical devices, you must follow the aforementioned sections in 21 CFR parts 820 and 1271.160(b)(1) and (b)(2).

An example of a CGTP requirement in which there is no corresponding section of the QS regulation is the CGTP requirement prohibiting pooling in § 1271.220(b). HCT/Ps regulated as medical devices that are from two or more donors may not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

F. Am I responsible for following all of the CGTP requirements?

You will find that many of the requirements are qualified by "where appropriate." A requirement is deemed to be "appropriate" unless you can document justification otherwise. What this means is that each establishment has the flexibility to determine if the requirement is appropriate for your establishment. A requirement is "appropriate" if nonimplementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable diseases, or in your inability to carry out any necessary corrective action. In general, a requirement is "appropriate" if it helps you to ensure that the HCT/P is not contaminated or cross-contaminated or if it helps you to carry out any needed corrective actions (§ 1271.150(e)).

For example, an establishment that processes HCT/Ps has determined that the § 1271.195(a)(1) environmental monitoring requirement for temperature and humidity control is not applicable because the establishment determined that the temperature and humidity would not affect the introduction, transmission or spread of communicable disease. If you determine that a requirement is not appropriate for your establishment, you must document justification of that determination (§ 1271.150(e)).

IV. EXEMPTIONS AND ALTERNATIVES (§ 1271.155)

A. How do I request an exemption or alternative from part 1271, subpart C or D?

Under § 1271.155(d), you must ordinarily request an exemption or alternative in writing (hardcopy or electronically). The request must be accompanied by all relevant valid

scientific data and either information justifying the requested exemption from the requirement (§ 1271.155(b)(1)) or a description of a proposed alternative method of meeting the requirement (§ 1271.155(b)(2)).

You may request an exemption orally in emergency situations when there is limited time to implement the exemption or alternative (§ 1271.155(d)). You must follow an oral request with an immediate written request (§ 1271.155(d)) with documentation that includes all relevant valid scientific data to support the request (§ 1271.155(b)).

Only after we grant the request may you begin operating under the exemption or alternative (§ 1271.155(e)). You must keep the hard copy documentation of approval from FDA and the date on which you began operating under such approval at the establishment (§ 1271.155(f)). We describe the procedures used to address requests for exemptions and alternative procedures in SOPP 9151 (Ref. 3).

B. Where do I send a request for an exemption or alternative?

Submit your request to the Director of the appropriate FDA center. If the HCT/P is regulated solely under § 1271.10 as a 361 HCT/P, as a biological product or a medical device regulated by the Center for Biologics Evaluation and Research (CBER), send your request to the Director, CBER. If the HCT/P is regulated as a medical device by the Center for Devices and Radiological Health (CDRH), send your request to the Director, CDRH. We provide more specific information on the process, including addresses and contacts, at http://www.fda.gov/cber/tissue/exemptionstis.htm.

C. Can an exemption or alternative apply to more than one establishment?

A granted exemption or alternative is only applicable to the establishment that requested it. However, if it affects the work performed by an establishment under contract to the exempted establishment, the information about the exemption or alternative should be shared with the contract establishment. A registered establishment could request an exemption or alternative that would apply to itself and a physically separate establishment (having different registration FDA Establishment Identifiers) under the same corporate management.

V. ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM (§ 1271.160)

A. What is a quality program?

Under § 1271.3(hh), a quality program is 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.

B. Which establishments must establish and maintain a quality program?

Any establishment that performs any step in the manufacture of HCT/Ps must establish and maintain a quality program that must be appropriate for the manufacturing steps performed and the specific HCT/Ps manufactured (§ 1271.160(a)). "Establish and maintain" means to define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis (§ 1271.3(cc)). For example, the quality program for a recovery establishment could include establishing and maintaining procedures to ensure that a donor's relevant medical records, including the physical assessment, are complete.

Each establishment has the flexibility to devise its own quality program, depending upon the functions it performs, and the HCT/Ps it manufactures.

C. What is the role of the quality program regarding procedures?

Under § 1271.160(b)(1), among other requirements, the quality program must ensure that the establishment complies with the requirements for procedures, appropriate to meet core CGTP requirements, in § 1271.180. A quality program also must ensure the review, approval and revision of procedures
(§ 1271.160(b)(1)).

D. What must I do when information is received from sources outside the establishment, and what must I do with this information?

The quality program must ensure that the establishment has procedures for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints (§ 1271.160(b)(2)). You could receive this information before or after distribution of the HCT/P (e.g., complaints from the consignee or results of communicable disease tests performed by other establishments that recovered HCT/Ps from a shared donor).

Example: An HCT/P establishment receives information from another establishment that a shared donor tested reactive for Hepatitis C Virus (HCV), with an FDA-licensed HCV nucleic acid test approved for cadaveric specimens. The establishment should investigate and evaluate the information received to determine if the HCT/P from this donor could potentially result in the transmission of a relevant communicable disease. The reactive test results for a relevant communicable disease agent or disease would mean that the donor is ineligible to donate (§ 1271.80(d)(1)). In this case, the establishment's quality program must ensure that procedures exist for all of the following:

- the quarantine of any HCT/Ps in the establishment's inventory from the same donor (§ 1271.160(b)(2)(iii)).
- the notification of all entities to whom the HCT/P was distributed (§ 1271.160(b)(2)(iii)). We recommend that this notification include written notification of the facts of the case (i.e., the reactive test results, the other establishment's additional test results, and additional testing that will be or has been performed on archived specimens, and the results when known).
- the recall of the HCT/P, and/or reporting to FDA (§ 1271.160(b)(2)(iii)) as necessary. We recommend that recalls be reported to the FDA district office's recall coordinator.

In addition, we recommend that establishments instruct all consignees on procedures for return of unused HCT/Ps.

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?

Under § 1271.160(b)(2), your quality program must ensure that procedures exist to share any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with the following:

- other establishments that are known to have recovered HCT/Ps from the same donor (§ 1271.160(b)(2)(i)); and
- other establishments that are known to have performed manufacturing steps with respect to the same HCT/P (§ 1271.160(b)(2)(ii)).

Relating to consignees, in the case of such information received after the HCT/P has been made available for distribution, shipped to the consignee, or administered (implanted, transplanted, infused or transferred) to the recipient, procedures must include provisions for assessing risk and appropriate follow-up, and evaluating the effect this information has on the HCT/P and for the notification of all entities to whom the affected HCT/P was distributed, the quarantine and recall of the HCT/P, and/or reporting to FDA, as necessary (§ 1271.160(b)(2)(iii)).

Example 1: An eye bank receives test results that are positive or reactive (even if that particular test is not recommended by FDA) for a communicable disease. The eye bank evaluates this information and determines that this new information concerns a potential increase in the risk of communicable disease transmission by the HCT/P. The eye bank shares this information with the establishment, an organ procurement organization (OPO) that recovers organs and other HCT/Ps. The OPO must inform processing establishments that received HCT/Ps from the same donor. The eye bank already has released the corneas, so it must notify its consignees.

Example 2: A recovery establishment has contracts with multiple processing establishments to recover HCT/Ps for them. When the recovery establishment receives information from one processing establishment that a recipient of an HCT/P from a shared donor had developed a serious infection, the recovery establishment is responsible for sharing this information with the other processing establishments that received HCT/Ps from the same donor (§ 1271.160(b)(2)(iii)). We recommend that these procedures be defined in your contracts, agreements, and other arrangements with other establishments.

F. How can a quality program ensure that appropriate corrective actions related to core CGTP requirements are taken, when necessary?

The quality program must ensure that appropriate corrective actions relating to core CGTP requirements are taken and documented and verify that such corrective actions are effective and in compliance with CGTP requirements (see § 1271.160(b)(3)). The corrective action should not adversely affect other operations. Where appropriate, corrective actions must include both short-term action to address the immediate problem, and long-term action to prevent the problem's recurrence (§ 1271.160(b)(3)).

You must document (where appropriate) the following:

- identification of the HCT/P affected and a description of its disposition (§ 1271.160(b)(3)(i));
- the nature of the problem requiring corrective action (§ 1271.160(b)(3)(ii));
- a description of the corrective action taken (§ 1271.160(b)(3)(iii)); and
- the date(s) of the corrective action (§ 1271.160(b)(3)(iv)).

G. What must the quality program ensure regarding personnel?

The quality program must ensure that personnel involved in activities related to core CGTP requirements have proper training, 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)).

Examples of how the quality program could ensure that personnel are properly trained and educated could include establishing training and education criteria for specific positions. This might be accomplished by ensuring that the content of training is relevant for an individual performing specific activities related to core CGTP requirements and by requiring a certain level of education and/or certification, as appropriate. For example, you may want to establish that personnel performing recoveries are certified by a professional organization.

H. How does the quality program ensure that appropriate monitoring systems are in place?

Under § 1271.160(b)(5), your quality program must establish and maintain appropriate monitoring systems as necessary to comply with requirements in part 1271, subpart D. For example, you might develop systems within the facility for environmental control (§ 1271.195(a)) (e.g., systems to monitor temperature and humidity), environmental monitoring (1271.195(c)) (e.g., viable particulate monitoring in a clean room), and storage (§§ 1271.260) (e.g., systems that monitor the temperature of HCT/P storage units and alarm when out of range).

I. When HCT/P deviations occur, what is the role of the quality program?

Under § 1271.160(b)(6), the quality program must investigate and document HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and make reports if required under § 1271.350(b) or other applicable regulations. Each investigation must include a review and evaluation of the HCT/P deviation, the efforts made to determine the cause, and the implementation of corrective action(s) to address the HCT/P deviation and prevent recurrence.

Example: HCT/Ps are recovered but later review of donor records indicate that the donor did not meet certain donor criteria stated in your establishment's SOPs. The recovered HCT/Ps are destroyed after processing and before distribution. This event is an HCT/P deviation related to core CGTP requirements that must be investigated and documented under § 1271.160(b)(6), but it is not necessary to report the deviation to FDA, under § 1271.350(b), because the HCT/Ps were not distributed.

J. What are the requirements for performing quality audits of your establishment?

Under § 1271.160(c), you must periodically perform for management review a quality audit of activities related to core CGTP requirements. We recommend that a quality audit be conducted at least annually, and more frequently, if necessary. A quality audit is a documented, independent inspection and review of the establishment's activities related to core CGTP requirements (§ 1271.3(gg)). The audit verifies compliance with the core CGTP requirements, by examining and evaluating objective evidence. We consider an inspection and review to be independent when it is performed by an individual who does not have direct responsibility for the matter being audited or is external to the audited establishment.

K. Will FDA review the quality audit during inspection of the establishment?

It is not our current policy to review or copy your actual quality audit reports during routine inspections and investigations except in certain limited circumstances (FDA

Compliance Policy Guide 130.300, Ref. 4). However, you should have a mechanism to demonstrate to the FDA investigator that quality audits are performed.

L. If the establishment relies on computer software to comply with core CGTP requirements, what activities must be performed before implementing the software?

If the computer software is either custom software (designed specifically for you) or commercially available software that has been customized or programmed for you (e.g., to perform a user-defined calculation or create a table), you must validate the software for its intended use. If the computer software used to comply with core CGTP requirements has not been customized, but rather is off-the-shelf software that has not been modified, then you must verify the performance of the software for its intended use. You must approve and document these activities (§ 1271.160(d)). If the software is being used for functions other than those related to core CGTP requirements, there is no requirement to either validate or verify.

Validation means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled (§ 1271.3(kk)), (e.g., a process consistently produces an HCT/P that meets its predetermined specifications). Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (§ 1271.3(ll)).

Example 1: An establishment develops its own computer software to store information used to make donor eligibility determinations (a core CGTP requirement). The establishment must validate its software for this intended use (§ 1271.160(d)).

Example 2: An establishment uses a computer-generated labeling system, such as bar-coding, developed by a software company for a different intended use, such as labeling blood products. Since labeling controls (§ 1271.250(a) and (b)) are core CGTP requirements, and the establishment is using the software for its own intended use, the establishment must validate the software for this intended use (§ 1271.160(d)). You could refer to FDA's Guidance for Industry and FDA Staff entitled, "General Principles of Software Validation" (Ref. 5).

Example 3. An establishment uses a commercial electronic spreadsheet to record donor testing results which are used to make a donor eligibility determination. Since the software has not been modified, you must verify that it performs this activity correctly (§ 1271.160(d)).

VI. PERSONNEL (§ 1271.170)

A. What are the specific requirements for personnel at HCT/P establishments?

You must have sufficient personnel to ensure compliance with the 21 CFR part 1271 requirements, and the personnel must have the necessary education, experience, and training to ensure competent performance of their assigned functions (§ 1271.170(a) and (b)). You should determine the qualifications needed to perform manufacturing functions in your establishment(s) and should reflect these qualifications in a job/position description. In addition, personnel must perform only those activities for which they are qualified and authorized (§ 1271.170(b)). You must train all personnel, and re-train as necessary, to perform their assigned responsibilities adequately (§ 1271.170(c)).

Example: Personnel working for a recovery establishment should be trained in how to perform a recovery, perform a physical assessment of the donor, and draw a blood specimen for communicable disease testing. As part of that training, personnel should be made aware of the possible consequences of improper performance of their activities, (e.g., the risk of transmission of communicable disease agents and diseases). An individual under contract agreement or other arrangement to a registered recovery establishment who performs these functions does not have to register independently (§ 1271.15(f)).

B. How would I ensure that personnel have the necessary education, experience and training to perform their job?

We recommend that you periodically review the qualifications, including training and professional development, of your personnel, not just when they are hired and initially trained, to ensure that they maintain skills necessary to perform their job. Some examples of evaluation tools you could use to ensure that your personnel have the necessary education, experience and training include:

- developing criteria for each position and ensuring that personnel meet and continue to meet such criteria; and
- setting up a program for demonstration of competency for their assigned functions when observed by a supervisor.

VII. PROCEDURES (§ 1271.180)

You must establish and maintain procedures appropriate to meet core CGTP requirements (listed in section III.A of this guidance) for all steps that you perform in the manufacture of HCT/Ps. You must design these procedures to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases through the use of HCT/Ps (§ 1271.180(a)).

A. What do I need to do before implementing new procedures related to core CGTP requirements?

Before implementation, you must have a responsible person review and approve new procedures (§ 1271.180(b)). You must also ensure the periodic review, approval and revision of procedures, and ensure compliance with the requirements of § 1271.180 with respect to such procedures as a function of your quality program (§ 1271.160(b)(1)).

B. Do procedures have to be physically maintained in the area where the operation is performed?

Procedures must be readily available to personnel in the area where operations are performed. However, procedures do not have to be physically maintained in the area of operation if such availability is impractical (§ 1271.180(c)).

For example, copies (e.g., on paper, or electronic media) of recovery SOPs could travel to recovery sites with personnel or could be accessed electronically from a separate location, as long as they are easily accessible to all employees performing recovery. Also, for example, it may not be feasible to physically keep SOPs in clean rooms where processing operations occur, because the SOPs could cause contamination of HCT/Ps. In that case, you could keep the SOPs in an adjacent area outside the clean room.

C. May I use procedures from established industry standards?

Yes, provided that you verify that the procedures, whether followed in their entirety or if modified by your establishment, meet the requirements of part 1271 and are appropriate for your operations (§ 1271.180(d)).

VIII. FACILITIES (§ 1271.190)

A. What are general requirements for HCT/P facilities?

Under § 1271.190(a), any facility used in the manufacture of HCT/Ps 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. You must maintain the facility in a good state of repair. You must provide lighting, ventilation, plumbing, drainage, and access to sinks and toilets that are adequate to prevent the introduction, transmission, or spread of communicable disease.

B. What facility cleaning and sanitation issues must I consider?

Under § 1271.190(b), you must maintain any facility used in the manufacture of HCT/Ps in a clean, sanitary, and orderly manner to prevent the introduction, transmission, or

spread of communicable disease. You also must dispose of sewage, trash, and other refuse in a timely, safe, and sanitary manner.

We recommend that you have a cleaning program supported by environmental monitoring, where appropriate, as described in §§ 1271.160(b)(5) and 1271.195(c). You should determine the appropriate frequency, method, and concentration of disinfectants to ensure prevention of contamination and cross-contamination in your facility.

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 these parameters have been achieved during each cleaning.

C. Is it necessary to perform different operations in separate areas within a facility?

Under § 1271.190(c), you must divide a facility used in the manufacture of HCT/Ps into separate or defined areas of adequate size for each operation that takes place in the facility, or you must establish and maintain other control systems to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of HCT/Ps to communicable disease agents.

It is not necessary that there be a separate designated room for each task performed during the manufacture of an HCT/P. You should evaluate the type of area that a task would require in order to prevent contamination or cross-contamination of HCT/Ps and designate an appropriate area for those tasks.

For example, it would not be appropriate to utilize a clean-room normally used for processing HCT/Ps to perform the following activities:

- preparing packaged, recently recovered HCT/Ps for shipment to another facility;
- prepackaging freshly recovered HCT/Ps for subsequent quarantine;
- handling (e.g., centrifugation, serum/plasma separation) of blood specimens to be used for infectious disease testing; or
- decontaminating instruments used for recovery or processing.

D. What facility-related procedures must I establish and maintain?

Section 1271.190(a) and (b) requirements are core CGTP requirements (§ 1271.150(b)(1)). Therefore, you must establish and maintain procedures in accordance with § 1271.180. In addition, § 1271.190(d)(1) requires that you establish and maintain procedures for facility cleaning and sanitation for the purpose of preventing the introduction, transmission, or spread of communicable disease. These procedures must

assign responsibility for sanitation and must describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility.

E. What facility-related documentation must I maintain?

In addition to the records required under § 1271.270, (see Section XIX of this guidance), § 1271.190(d)(2) requires that you document, and maintain records of all cleaning and sanitation activities performed to prevent contamination of HCT/Ps. You should create these records concurrently with cleaning and sanitation activities. You must retain such records 3 years after their creation (§ 1271.190(d)(2)).

F. How do facility-related requirements apply to recovery of HCT/Ps?

The facility-related requirements apply to recovery of HCT/Ps. You should determine how to evaluate an area used for recovery in order to prevent contamination and cross-contamination, according to the general facilities requirements under § 1271.190(a). As these recovery facilities may not be under your day-to-day control, you should establish and maintain procedures to prevent the introduction, transmission, or spread of communicable disease that may be implemented during each recovery. You should consider the following elements:

- the facility offers a suitable size, location, and is constructed so that an aseptic recovery can be successfully performed;
- there is limited access to the recovery site during recovery;
- the site is in a good state of repair;
- there is adequate lighting and space;
- ventilation and airflow is adequate (e.g., no open windows, vent is not located directly above the recovery operations);
- there is access to running water and a sink;
- all working surfaces used for the recovery operations are cleaned with verified cleaning agent and the cleaning documented before recovery; and
- aseptic technique can be adequately performed.

A description and/or a checklist could be used to document that the recovery location meets established, desired parameters each time a recovery is performed. The location of the recovery should be documented.

IX. ENVIRONMENTAL CONTROL AND MONITORING (§ 1271.195)

A. What environmental controls must I have in place at my facility?

Under § 1271.195(a), where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, you must adequately control

environmental conditions and provide proper conditions for operations. Where appropriate, you must provide for the following control activities or systems:

- temperature and humidity controls;
- ventilation and air filtration;
- cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
- maintaining equipment used to control conditions necessary for aseptic processing operations.

We are not recommending clean room classification requirements for particular facilities or manufacturing steps. You should determine the appropriate level of control. The appropriate level of control may depend on such factors as which manufacturing steps are involved, whether they are performed in an open or closed system, whether they are performed in a laminar flow hood or Biological Safety Cabinet, and other factors as described in FDA "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (Ref. 6). This guidance could provide useful information to an HCT/P establishment that is developing procedures on environmental control and monitoring. Also, chapter <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments in US Pharmacopoeia 30 (Ref. 7) contains information on environmental monitoring.

We recommend that you determine the types of microorganisms that could exist in your facility and design your cleaning, and environmental control and monitoring programs accordingly. You should select the types of disinfectant/cleaning agents to use that are effective against microorganisms you have identified.

Example: An eye bank recovers whole globes. We recommend that processing (i.e., removal of the cornea from the whole globe) be performed in a laminar flow hood or Biological Safety Cabinet because this equipment provides a controlled environment and can be adequately cleaned and monitored.

B. How often must I inspect my environmental control systems?

Under § 1271.195(b), you must inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You must take appropriate corrective action as necessary.

C. Is environmental monitoring required?

Under § 1271.195(c), you must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms.

For example, we recommend that you perform periodic monitoring of non-viable and viable particulates, work surfaces, and personnel. This monitoring should be performed in clean rooms using LFHs and BSCs for processing in order to evaluate environmental changes that may increase the likelihood of contamination or cross-contamination of HCT/Ps.

D. What temperature and humidity factors should be considered for environmental control and monitoring?

Each establishment has the flexibility to determine if temperature and humidity could reasonably be expected to have an adverse effect on the HCT/Ps it manufactures. For example, if steps in the manufacture of HCT/Ps have identifiable parameters for maintaining a certain temperature and/or humidity, or the performance of the reagents used in the manufacturing of HCT/Ps could be adversely affected by temperature and/or humidity over the length of storage of the reagent or product, you must adequately control and monitor environmental conditions and provide proper conditions for operations (see § 1271.195(a) and (c)).

E. How often should I perform environmental monitoring?

Under 1271.195(c), you must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Under 1271.195(b), you must inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You have the flexibility to design your environmental monitoring system for the type of operations and particular environmental factors in your facility.

We recommend that you define the type and frequency of environmental monitoring to be performed, including the monitoring used to verify that cleaning procedures are adequate, and that the environmental control systems are capable of maintaining the degree of control specified. We recommend that you define alert and action levels for test results and specify potential corrective actions when alert and/or action levels are exceeded. The following types of environmental monitoring should be considered in clean rooms, laminar flow hoods, and Biological Safety Cabinets used for processing:

- non-viable particulate air monitoring;
- viable particulate air monitoring;
- clean area positive pressure levels;
- surface monitoring (taking into account all different surfaces in the manufacturing environment): and
- personnel monitoring (e.g., gloves).

F. Are records related to environmental control and monitoring required?

You must document and maintain records of environmental control and monitoring activities under § 1271.195(d). In addition, under § 1271.270, you must retain records concurrently with the performance of each step required in 21 CFR part 1271, subparts C and D, including the environmental control and monitoring activities required under § 1271.195(a) through (c). We also note that the requirements for environmental control under § 1271.195(a) are core CGTP requirements (§ 1271.150(b)(2)).

G. What procedures related to environmental control and monitoring must I establish and maintain?

Requirements related to environmental control in § 1271.195(a) are core CGTP requirements (§1271.150(b)(2)). Therefore, you must establish and maintain procedures in accordance with § 1271.180. The regulations do not set forth specific procedures for environmental monitoring. However, for environmental monitoring that you conduct in accordance with § 1271.195(c), we recommend that you specify the type and frequency of environmental monitoring, define alert and action levels for test results, and specify potential corrective actions when alert and/or action levels are exceeded (see section IX.E.).

H. What environmental control and monitoring issues should be considered for recovery of HCT/Ps?

Environmental control and monitoring considerations during recovery operations are similar to those of other manufacturing steps. You must consider the need for environmental control and monitoring of facilities used for HCT/P recovery (see § 1271.195(a) and (c)). Requirements relating to recovery in § 1271.215 are core CGTP requirements (§1271.150(b)(5)). Therefore, you must establish and maintain procedures in accordance with § 1271.180 to prevent contamination or cross-contamination during recovery, or circumstances that otherwise increase the risk of the introduction, transmission or spread of communicable disease through the use of the HCT/P. While environmental monitoring might not have to be performed at each recovery site, you must have controls in place to provide assurance that the site of recovery does not increase the potential for contamination and cross-contamination of HCT/Ps (see § 1271.195). You should set specific parameters for recovery site suitability and verify for each recovery that these parameters have been met. A controlled environment, such as an operating room setting, is recommended but not required. If other types of facilities are used for recovery, adequate temperature and humidity controls, and adequate ventilation must be provided (§ 1271.195(a)(1) and (2)).

Information regarding recovery establishments for dura mater can be found in the document entitled "Guidance for Industry and FDA Staff, Class II Special Controls: Guidance Document: Human Dura Mater," in section 10: Manufacturing Controls, part B. Excision Facilities (Ref. 8). Specifically, we recommend that the recovery

establishment meet the standards of a surgical operating room at a minimum. This guidance recommends that recovery establishments should have:

- air filtration;
- stainless steel furniture;
- washable walls;
- refrigeration for donor storage;
- hypothermia blankets to cool the donor during the procedure; and
- single use or disposable instruments for each donor.

X. EQUIPMENT (§ 1271.200)

A. What are the general equipment requirements?

Under § 1271.200(a), equipment used in the manufacture of HCT/Ps must be of appropriate design for use and must be suitably located and installed to facilitate operations, including cleaning and maintenance, in order to prevent the introduction, transmission, or spread of communicable diseases. Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing in accordance with 21 CFR part 1271 must be capable of producing valid results. You must clean, sanitize, and maintain equipment according to established schedules.

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. You should consider the equipment's potential to control contamination and cross-contamination of HCT/Ps during use. We recommend you develop and execute an installation plan for equipment, if applicable, to ensure that the equipment is suitably located and installed (in accordance with the equipment manufacturer's specified requirements) and operates properly.

B. Do I have to qualify or certify equipment (Installation Qualification, Operational Qualification, Performance Qualification)?

Equipment qualification and certification are well established methods for ensuring that equipment can operate and produce desired results consistently. While § 1271.200 does not explicitly require equipment qualification and certification, it is long-standing industry standard practice to do so, particularly as part of process validation (FDA Guideline on General Principles of Process Validation, Sections VII and VIII) (Ref. 9). We recommend that you qualify and certify your equipment. You should routinely perform certification for certain equipment such as laminar flow hoods and Biological Safety Cabinets, according to the manufacturer's specifications.

Example: A laminar flow hood is generally certified when initially installed. Periodic recertification to ensure that the laminar flow hood is operating as intended could include

measuring the air flow and velocity, ensuring proper operation of the high efficiency particulate air (HEPA) filter (e.g., particle testing), and/or making sure that the exhaust is properly directed. 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.

C. Does recovery equipment (e.g., instruments) have to be segregated by donor prior to cleaning in an automated washer?

You are not required to segregate recovery equipment used for different donors prior to cleaning in an automated washer. It is acceptable to place multiple instrument trays into automated washers. If possible, it would be preferable to clean instruments used on the same type of tissue together in such loads (such as those used for musculoskeletal HCT/P recovery). You should ensure that automated washers operate consistently and that they are properly cleaned after each use according to established procedures.

D. Is there any prohibition on the re-use of cleaning/disinfection solutions, or containers used to clean and disinfect instruments?

As long as the manufacturer's instructions for use of cleaning/disinfection solutions allow for reuse, then it is acceptable to reuse such solutions. For most of these cleaning/disinfection solutions, the manufacturer's instructions give information about how frequently to change the solutions, varying from daily to weekly and/or when visually unsuitable. Containers used in instrument cleaning could also be reused as long as they are cleaned and sanitized after each use.

E. Are there special considerations for cleaning and sanitizing equipment at risk for Transmissible Spongiform Encephalopathy contamination?

While prion contamination is a significant concern, existing technology and current scientific information is limited regarding reducing the risk of transmissible spongiform encephalopathy (TSE) in surgical instruments used for HCT/P recovery and/or processing. There are no definitive recommendations for how to reliably perform TSE decontamination, nor procedures for rapidly identifying the presence of prions on instruments. However, we recommend that you use heightened screening and stringent recovery procedures. For example, where possible, consider using disposable instruments for recovery of HCT/Ps at high-risk for prion contamination, such as cornea and dura mater. You should consider establishing procedures to track instruments that were used on particular donors as well as instruments that are cleaned and sanitized together. FDA's Transmissible Spongiform Encephalopathy Advisory Committee advised on July 18, 2003, that instruments need not routinely undergo special cleaning procedures prior to sterilization, even if these instruments were used to recover or process high-risk HCT/Ps (Ref. 10). However, if a particular donor after recovery was found to have or was suspected of having a TSE, then the instruments used for recovery should be

destroyed. You must keep records of the instruments used in the recovery and/or processing of a donor's HCT/Ps (see §§ 1271.200(e) and 1271.270(a)).

F. What procedures and schedules are required for equipment?

Section 1271.200(a) requirements are core CGTP requirements (§ 1271.150(b)(3)). Therefore, you must establish and maintain procedures in accordance with § 1271.180. Under § 1271.200(b), you must establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of HCT/Ps to communicable disease agents, and other events that could reasonably be expected to result in the introduction, transmission, or spread of communicable diseases.

We do not specify cleaning schedules for equipment. Each establishment has the flexibility to determine and justify cleaning procedures that will prevent the introduction, transmission or spread of communicable diseases. Manufacturers' instructions for cleaning materials and equipment could provide useful information for determining appropriate cleaning schedules for your equipment.

For example, apheresis machines using disposable tubing may not require cleaning between each HCT/P recovery. However, if there is a spill, there should be special cleaning procedures in place.

G. What equipment calibration must I perform?

Under § 1271.200(c), where appropriate, you must routinely calibrate according to established procedures and schedules all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing. For example, an instrument used to monitor the temperature of an HCT/P storage unit must be regularly calibrated. Some equipment, such as computers, are not subject to calibration.

In order to determine an appropriate calibration schedule, you could consult the Operations Manual or contact the manufacturer of the equipment to determine and establish appropriate intervals for calibrating each piece of equipment. You should also take into consideration the specific use of this equipment within the manufacturing facility to determine if special conditions could warrant more frequent calibration than is recommended by the equipment manufacturer. Calibration accuracy should be traceable to accepted/known standards (e.g., National Institute of Standards and Technology, http://www.nist.gov/), or the manufacturer's supplied or recommended standard.

H. What equipment inspections must I perform?

Under § 1271.200(d), you must routinely inspect equipment for cleanliness, sanitation, and calibration, and to ensure adherence to applicable equipment maintenance schedules.

I. What records related to equipment must I keep?

Under § 1271.200(e), you must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with § 1271.200. 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. You must maintain records of the use of each piece of equipment, including the identification of each HCT/P manufactured with that equipment (§ 1271.200(e)). 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.

For example, for single-use instruments, you must maintain records of the use of that equipment, including the identification of each HCT/P manufactured with that equipment (see § 1271.200(e)). Maintaining records for the use of single-use instruments would be helpful, for example, to the HCT/P manufacturer in case the single-use device is recalled because the manufacturer discovered that the distributed devices were not sterile.

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. If it is necessary to implement an alternate method of identifying the current maintenance, cleaning, sanitizing and/or calibration status of each piece of equipment, the alternate method should permit the operator to easily check, prior to each use, that the equipment's maintenance, cleaning, sanitizing and/or calibration have been properly performed.

You may have another establishment perform equipment maintenance, cleaning, sanitizing, and/or calibration for you, under a contract, agreement or other arrangement. You may use the other establishment's records to demonstrate compliance with § 1271.200. However, you are still responsible for ensuring that the services provided are adequate and in compliance with applicable requirements (1271.150(c)(1)(ii) and (iii)).

See section XIX of this guidance (§ 1271.270) for further information about general recordkeeping requirements.

J. What are the responsibilties of recovery establishments that contract the cleaning and sterilization of recovery instruments (equipment)?

In order to demonstrate that cleaning and sterilization of recovery instruments performed by a contract facility are appropriate, the recovery establishment should:

- obtain and approve the procedures, and review the records of cleaning and sterilization per § 1271.200;
- establish and maintain verification procedures under § 1271.210 for any instruments cleaned and sterilized for you by a facility under contract, agreement or other arrangement; and
- have the procedures and records available for review on inspection.

Establishments that only clean and sterilize recovery instruments (equipment) under contract, agreement, or other arrangement to a registered recovery establishment are not required to register, because this function is not considered a manufacturing step.

XI. SUPPLIES AND REAGENTS (§ 1271.210)

A. What are supplies and reagents?

Supplies and reagents include all materials that are used during manufacture, not just those coming into direct contact with HCT/Ps. Examples of supplies include sterile drapes, gauze, cleaning swabs, alcohol pads, and instruments (equipment) that are cleaned and sterilized under contract, agreement or other arrangement for you. Examples of reagents include cleaning agents, saline, dimethyl sulfoxide, anticoagulants, and chemical and antibiotic solutions used in processing.

B. What verification is required for supplies and reagents?

Under § 1271.210(a), you must not use supplies and reagents until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent. Use of a contaminated or otherwise defective supply or reagent in the manufacture of an HCT/P could lead to such problems as the introduction of a communicable disease agent or the failure to properly preserve the HCT/P.

You or a vendor must verify that those supplies and reagents used in all steps of the manufacture of HCT/Ps (not only those that come in contact with an HCT/P), including recovery, meet specifications designed to prevent circumstances that increase the risk of introduction, transmission, or spread of communicable diseases (see § 1271.210(a)). You should store and use supplies and reagents according to the manufacturer's instructions. We recommend that you keep product information data sheets for all supplies and reagents used, update these sheets as products change, and keep an archive of previously used products. Verification that reagents meet specifications may be accomplished either by reviewing the Certificate of Analysis (COA) or by performing relevant testing. 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 for the supply, including any sterilization process. You

must maintain records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a COA from the vendor (§ 1271.210(d)(2)).

C. What are some methods to verify reagents or supplies?

If you receive supplies and/or reagents from a vendor or another establishment, you should verify that the vendor or other establishment has a system in place to certify that the supplies and/or reagents meet established specifications. You could reference specification sheets, COAs, and manufacturer's package inserts describing the reagent and/or supply to verify suitability.

If a processor requires that specific supplies and reagents be used by recovery establishments, then the processor should verify the supplies and reagents and should include this information in their contracts, agreements, or other arrangements with the recovery establishment.

Example: Supplies used to wrap or package the individual HCT/Ps at recovery should be designed to prevent leakage that could cause contamination or cross-contamination, and should be able to perform in this capacity when subjected to expected storage temperatures for that HCT/P type. 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.

D. Are reagents required to be sterile?

Under § 1271.210(b), reagents used in processing and preserving HCT/Ps must be sterile, where appropriate.

Example: Non-sterile water might be appropriate for use during processing prior to terminal sterilization of the HCT/P if the water meets specifications determined for use during process validation.

E. What is required of reagents I produce in-house?

You must validate and/or verify the processes used for production of in-house reagents (§ 1271.210(c)). For example, in the case of reagents produced for disinfecting recovery processes, the recovery establishment must verify that these reagents meet specifications designed to prevent the introduction, transmission or spread of relevant communicable disease agents or diseases (e.g., solutions are sterile, have the proper concentrations, and fall within a specific pH range).

F. What records must I keep related to supplies and reagents?

Under § 1271.210(d), you must maintain the following records pertaining to supplies and reagents:

- records of the receipt of each supply or reagent, including the type, quantity, manufacturer, lot number, date of receipt, and expiration date;
- records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a COA from the vendor; and
- records of the lot of supply or reagent used in the manufacture of each HCT/P.

You should establish a system under which particular lots of supplies and reagents can be linked to individual HCT/Ps. This does not necessarily require an individual record for each supply used in preparing every HCT/P (e.g., sterile drapes and gloves). For instance, you may track those supplies by recording dates between which certain lot numbers were used, rather than individually recording each supply as it is used during the manufacture of each HCT/P. Maintaining the records required in § 1271.210(d)(3) will enable you to determine which lots of supplies and reagents were used at a particular time and which HCT/Ps were manufactured during that same time period. This would facilitate a recall of HCT/Ps if supplies or reagents used in their manufacture are later found to increase the risk of introduction, transmission, or spread of communicable diseases.

G. What procedures related to supplies and reagents must I establish and maintain?

Section 1271.210(a) and (b) requirements are core CGTP requirements (§ 1271.150(b)(4)). Therefore, you must establish and maintain procedures in accordance with § 1271.180.

XII. RECOVERY (§ 1271.215)

Recovery means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer (§ 1271.3(ii)). If you are an establishment that recovers HCT/Ps, you must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P (§ 1271.215).

In general, establishments that recover HCT/Ps must register with FDA (§ 1271.10(b)). However, if you, the registered establishment, contract with or have an agreement or other arrangement with an individual to recover tissue (e.g., ocular tissue) or cells (e.g., cord blood)) for you and send the HCT/P to you for processing, that individual does not have to register or list

independently. That individual must comply with all other applicable requirements in 21 CFR part 1271 (§ 1271.15(f)).

A. What procedures and records related to recovery are required?

Section 1271.215 requirements are core CGTP requirements (§ 1271.150(b)(5)). Therefore, you must establish and maintain procedures in accordance with § 1271.180. You must also establish and maintain procedures for other core CGTP requirements related to recovery operations where appropriate, such as:

- facilities (§§ 1271.190(a) and (b));
- environmental control (§ 1271.195(a));
- equipment (§ 1271.200(a));
- supplies and reagents (§§ 1271. 210(a) and (b));
- labeling controls (§§ 1271.250(a) and (b));
- storage (§§ 1271.260(a) through (d)); and
- receipt, predistribution shipment, and distribution of an HCT/P (§§ 1271.265(a) through (d)).

Your quality program must address all of these core CGTP requirements (§ 1271.160(b)). Maintenance of records and a record management system must be in compliance with §§ 1271.270.

B. What are some ways that a recovery establishment could ensure that HCT/Ps are recovered in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease?

You should evaluate all recovery-related operations to determine how these activities can be performed to control contamination and cross-contamination, including the following:

- technical procedures used;
- personnel involved;
- equipment, supplies, and reagents that are used during recovery; and
- facilities where recoveries take place (See section VIII F. of this guidance).

Specific examples include:

- Staff must have the experience, education and training necessary to perform recovery operations (see § 1271.170).
- Recovery site suitability parameters must be established and documented, including facility cleaning and maintenance, and environmental controls (see §§ 1271.190 and 1271.195).

- Specific body cooling parameters including time and temperature limits for recovery should be established. For example current industry standards recommend that the time limit for tissue recovery should not exceed
    - 24 hours after death if the body is cooled or refrigerated within 12 hours of death; or
    - 15 hours after death if the body was not cooled or refrigerated.
- Recovery should be performed using aseptic technique.
- Recognized, published industry practices appropriate to controlling contamination (e.g., zone recovery, isolation draping, sequencing) should be utilized.
- HCT/Ps should not be recovered from an area of the body where there is localized infection.
- Equipment used in the manufacture of HCT/Ps must be of appropriate design for its use (§ 1271.200(a)); we consider equipment to include instruments. You must clean, sanitize, and maintain equipment according to established schedules (§ 1271.200(a)). You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with § 1271.200 (§ 1271.200(e)).
- Supplies and reagents used during recovery must be in compliance with § 1271.210(a) through (c) and records must be maintained in compliance with § 1271.210(d).
- Recovery activities and problems related to microbial contamination should be evaluated (e.g., technical errors, pre-processing culture results should be tracked and trended).

C. What are ways in which a recovery establishment could identify the donor prior to HCT/P recovery?

Verifying and documenting the donor identity is the first step in HCT/P tracking and is critical for preventing the spread of communicable disease agents or diseases by ensuring that donor eligibility information corresponds to the actual donor of the HCT/Ps (see 1271.270(a)). Prior to recovering HCT/Ps from a deceased donor, you should compare the potential donor's identification with the donor's name as stated on the consent/authorization document and relevant medical records, and compare other identifiers such as age, sex, race, and weight.

You should ask living donors to verify their name prior to HCT/P collection. You should document the methods used to verify the donor identity and should include the source of the verification information (e.g., photo ID such as a driver's license, hospital ID tag or band, identification by appropriate recovery site personnel, living donor's statement of his/her name), the date and time at which the identification was made, and the name of the recovery staff member(s) who made the identification. For deceased donors, you could reproduce the donor's identification tag or band by photographing it documenting its content.

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?

A processor could periodically audit the records provided by the recovery establishment by comparing them to other publicly available information related to the donors and/or could contact the physicians referenced in the donor records. 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)

If you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P (§ 1271.220(a)).

A. What is processing?

Under § 1271.3(ff), processing means 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.

In the context of this guidance, the set of processing activities that an establishment performs on an HCT/P taken together would be considered a process and would be subject to regulations such as §§ 1271.220, 1271.225, and 1271.230.

Example 1: Corneal processing could include separation of the corneoscleral rim from the globe following enucleation (removal of the eye), 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 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.

Example 4: Processing steps for musculoskeletal HCT/Ps could include removal of blood and lipids through chemical or physical means, various chemical and/or antibiotic soaks and washes, machined shaping of the bone, and the use of gamma irradiation as a bioburden reduction or terminal sterilization method.

Processing also includes obtaining specimens that are subsequently sent for microbiological testing (e.g., collection of swab specimens or representative HCT/Ps for destructive cultures), and the actual microbiological testing, including speciation of microorganisms that are detected.

B. May I pool HCT/Ps?

1. Pooling HCT/Ps from two or more donors

Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing (§ 1271.220(b)). For example, commingling bones from different donors during processing would be considered pooling. Pooling does not include the sequential transplantation of HCT/Ps (e.g., bone, skin) from different donors or the sequential administration of cellular products (e.g., cord blood) from different donors. In the event that you determine that pooling of HCT/Ps from two or more donors is necessary to obtain a therapeutic dose, you may request an exemption or alternative under § 1271.155.

2. Pooling HCT/Ps recovered at different times from one donor

In general, we discourage the practice of pooling cellular products that were collected from a single donor at different points in time during processing or post-thaw because of the increased risk that one product could be contaminated and could cross-contaminate the other. However, § 1271.220(b) does not prohibit the practice of pooling cellular products that were collected from a single donor as long as the processing otherwise complies with the applicable requirements and the tracking/labeling systems are well-controlled in order to prevent mix-ups.

C. What in-process control and testing must I perform?

Under § 1271.220(c), you must ensure that specified requirements, consistent with the general requirements of § 1271.220(a), for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or until necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

You should establish appropriate, objective mechanisms to control and monitor each process to ensure that you are processing HCT/Ps in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P. You could use a variety of methods for controlling and monitoring your processes including, statistical process-control methods, review of product acceptance criteria and results, as well as a meaningful quality audit.

Section 1271.220(c) requires in-process control and testing. To be in compliance with this section you could check the results of testing at various steps in processing (for example, by sampling in-process HCT/Ps). The sample selected for testing (e.g., culture) must be representative of the HCT/P to be evaluated (§ 1271.220(c)). This may not be the case if a small sample of the 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 (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 should be conducted because they are a critical in-process control for musculoskeletal (e.g., bone, tendon, ligament) HCT/Ps. 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[7] 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.

A disinfection or sterilization process must be validated based on the capability of that process to reduce or eliminate an expected level and mix of microorganisms on the particular products that will be put through the process. 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), 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.
Pre-processing cultures play a critical role in monitoring the process input to ensure that the process capability will not be affected. However, as discussed during the October 11-12, 2007, FDA/Centers for Disease Control and Prevention workshop entitled,

[7] The Tissue Safety Team consists of CBER representatives from several Offices and the primary purpose is to provide a coordinated process for the review, investigation and communication of reports of HCT/P adverse reactions.

"Processing Methods for Orthopedic, Cardiovascular, and Skin Allografts",[8] and acknowledged in section 5.4.1 of the Association for the Advancement of Medical Instrumentation (AAMI)'s new technical information report (TIR37:2007),[9] current microbiological testing methodologies present unique challenges that can be difficult to overcome. In particular, current methods for sampling HCT/Ps are limited. Furthermore, certain microorganisms are difficult to culture, so if they are present on/in an HCT/P at low levels, testing may not detect them. Thus, even when working with a validated process, processors should bear these limitations in mind as they plan pre-processing cultures and as they assess the results.

We recommend that 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.

- Do not process any musculoskeletal HCT/Ps from a donor that has any 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}.

- Do not process any musculoskeletal HCT/Ps from a donor who has multiple pre-processing cultures positive for enteric or pathogenic microorganisms, unless you have a terminal sterilization process validated to a SAL of 10^{-6}.

E. Are HCT/Ps required to be sterile?

We do not require that HCT/Ps be sterile, but you should use aseptic technique during manufacturing to prevent contamination and cross-contamination. It is the current industry practice to use aseptic technique during recovery and processing. Each step used in the processing of HCT/Ps must be controlled to prevent the introduction, transmission, or spread of communicable disease agents (see § 1271.220(a)).

F. What special processing and process-control considerations must I have for dura mater?

For dura mater, when there is a published validated process that reduces the risk of TSE, you must use this process (or an equivalent process that you have validated), unless this process adversely affects the clinical utility of the dura mater (§ 1271.220(d)(1)).

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[8] Transcript available at http:www.fda.gov/cber/tissue/min.htm.

[9] The referenced document is an AAMI technical information report (TIR), entitled "Sterilization of health care products – Radiation – Guidance on sterilization of human tissue-based products," which published on November 20, 2007. The TIR is available at http:www.aami.org.

Furthermore, when you use a published validated process, you must verify such a process in your establishment (§ 1271.220(d)(2)).

We realize that validated methods for reducing TSE infectivity are not currently being used on human dura mater, and that there are no validated methods currently available that do not decrease the clinical utility of dura mater. Therefore, § 1271.220(d) requires use of a validated process when one is published.

As new validated processes become available, they will be published in the literature. You do not have to validate a published procedure, rather, you could verify that a previously validated process has been fully and properly implemented in your establishment. We recognize that processing methods could be developed that reduce the risk of TSE but that render the HCT/P unsuitable for its intended use. Accordingly, you are not required to implement a process if it adversely affects the clinical utility of the dura mater. Alternatively, you could validate an equivalent procedure for use in your establishment that is at least as effective as a published procedure, without adversely affecting the clinical utility of the dura mater.

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" (Ref. 8).

XIV. PROCESS CHANGES (§ 1271.225)

Under § 1271.225, any change to a process must be verified or validated in accordance with § 1271.230 to ensure that the change does not create an adverse impact elsewhere in the operation, and must be approved before implementation by a responsible person with appropriate knowledge and background. You must communicate approved changes to the appropriate personnel in a timely manner. This provision does not apply to manufacturing steps other than processing. Changes to verified processes may require either verification or validation. However, under § 1271.230(c), you must review and evaluate the process and perform revalidation where appropriate (see Section XV.F of this guidance).

For example, a switch from one brand of a solution used in processing to another brand of solution would be a process change. In this situation, the establishment could verify that the new solution performs as intended in a manner that does not introduce, transmit, or spread communicable disease agents.

XV. PROCESS VALIDATION (§ 1271.230)

A. What are general requirements for process validation?

Under § 1271.230(a), where the results of processing described in § 1271.220 cannot be fully verified by subsequent inspection and tests, you must validate and approve the process according to established procedures. You must document the validation activities and results, including the date and signature of the individual(s) approving the validation.

B. What is the difference between validation and verification?

Validation means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or HCT/P meeting its predetermined specifications (§ 1271.3(kk)). Validation is performed before a process is used to manufacture HCT/Ps.

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (§ 1271.3(ll)). Verification of a process is performed after a process has been completed and is performed on all products undergoing the process. Examples of verification include the following:

Example 1. For sterilization of processing instruments using a standard cycle accepted by industry, verification could be accomplished by monitoring cycle parameters such as pressure, time, and temperature in each load, as well as by using biological indicators.

Example 2. Cleaning agents used for processing areas and equipment could be selected based on literature searches or Environmental Protection Agency (EPA) registration. Verification that the manufacturer's instructions are followed with respect to dilution and contact time is generally sufficient to meet the CGTP requirements.

Example 3. For processes that you design, validation will generally be required. This would entail establishing acceptance criteria for each processing step and determining through appropriate testing that these criteria can be consistently met. An adequately validated process that remains unchanged will generally need less in-process control and testing.

C. How do I perform a validation study?

The FDA regulations under 21 CFR part 1271 do not specify how to perform a validation study. The FDA "Guidance for industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation" (Ref. 12) provides information about validation. Another useful reference is "Guideline on General Principles of Process Validation" (Ref. 9). Validation studies conducted by your establishment or by experts in

the field could be acceptable. For example, you could obtain validation data to document the effectiveness of a process to prevent contamination in several ways, such as:

- verifying full and proper implementation of a previously validated procedure such as a procedure found in a technical manual of another organization;
- conducting literature searches to demonstrate that the procedures implemented are known to be effective in preventing infectious disease contamination (e.g., EPA-registered chemical sterilants for laboratory surfaces); or
- conducting off-line or on-line challenges with indicator organisms to evaluate the capacity of a process to prevent contamination.

Example: You are performing a validation study for your disinfection process (e.g., antibiotic soak). Such a study should include steps to address bacteriostasis and fungistasis due to residual processing agents that could result in false negative culture results.

D. What information should I collect for processes that must be validated?

You must ensure that you are using effective processes to prevent infectious disease contamination and cross contamination (see §§ 1271.145, 1271.220(a) and 1271.230(a)). We encourage you to evaluate your current validation data to ensure that they demonstrate that your processes will reliably prevent contamination and cross-contamination. In your evaluation, you should consider whether your procedures are effective as well as whether your validation is adequate.

For example, you should have information such as:

- whether cleaning agents and procedures used on processing equipment and surfaces are effective in removing or inactivating adventitious agents, so that HCT/Ps are not cross-contaminated; and
- whether there have been repeated instances where test results and/or adverse reaction reports indicate that the final product is contaminated.

E. What is required if I make a written representation that my processing methods reduce the risk of transmission of communicable disease by an HCT/P?

Under § 1271.230(b), any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to, a representation of sterility or pathogen inactivation of an HCT/P, must be based on a fully verified or validated process.

F. What must I do when I make changes to a validated process?

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. You must document these activities (§ 1271.230(c)). The requirements for changes to verified processes, as well as the approval and communication required for changes to either verified or validated processes is included in section XIV of this guidance.

Examples of process changes that would require validation include changing the following:

- 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 of a freeze-dryer where the change in cycle could reasonably be expected to cause contamination or cross-contamination.

XVI. LABELING CONTROLS (§ 1271.250)

A. What procedures must I establish and maintain to control the labeling of my HCT/Ps?

Section 1271.250(a) and (b) requirements are core CGTP requirements (§ 1271.150(b)(7)). Therefore, you must establish and maintain procedures in accordance with § 1271.180 to control the labeling of HCT/Ps. You must design these procedures to ensure proper HCT/P identification and to prevent mix-ups (§ 1271.250(a)). Examples of procedures that you could use to prevent mix-ups include the following:

- identifying dedicated work areas and controlling separation of activities;
- enclosing an extra label in the processing record as evidence of the actual label used (or for electronic systems you could retain an electronic copy);
- labeling the HCT/Ps from one donor at a time; and
- confirming that all extra labels or prelabeled containers issued for HCT/Ps obtained from a specific donor have been reconciled and removed from the work area.

B. What control procedures must I use to verify label accuracy, legibility, and integrity?

To ensure proper identification of HCT/Ps at every step of manufacturing, your procedures must include verification of label accuracy, legibility, and integrity

(§ 1271.250(b)). Each establishment has the flexibility to define the methods of control for complying with the requirements.

Example: One way to verify identification of donors and HCT/Ps at recovery would be to have multiple personnel examine the labels. If a recovery establishment uses hand-generated labels, one way to verify the accuracy and legibility is to use indelible ink and fixative to ensure label integrity.

C. What labeling requirements apply to my HCT/P?

Under § 1271.250(c) your procedures must ensure that each HCT/P is labeled in accordance with all applicable labeling requirements, including those in the following regulations

- records accompanying an HCT/P (§ 1271.55);
- HCT/Ps in quarantine (§ 1271.60);
- storage and use of HCT/Ps from a donor determined to be ineligible (§ 1271.65);
- HCT/Ps from donors excepted from the donor eligibility requirements (§ 1271.90);
- tracking of HCT/Ps (§ 1271.290); and
- labeling (§ 1271.370).

D. Do the CGTP regulations specify when labels are to be placed on HCT/P containers?

The labeling provisions in the CGTP requirements do not indicate the time frame for placing labels on HCTP containers, other than to specify how certain products must be labeled when they are made available for distribution (see §1271.370). Note that under §1271.250, you must design procedures to ensure proper HCT/P identification and to prevent mix-ups.

XVII. STORAGE (§ 1271.260)

A. What storage area activities must I control?

Under §1271.260(a), you must control your storage areas and stock rooms to prevent the following:

- mix-ups, contamination, and cross-contamination of HCT/Ps, supplies, and reagents; and
- an HCT/P from being improperly made available for distribution.

You should identify and design areas used for storage of HCT/Ps to facilitate monitoring of temperature and locating in-process HCT/Ps, quarantined HCT/Ps, and HCT/Ps that have been made available for distribution. Each storage area should have signs indicating the types of supplies, reagents, and HCT/Ps contained in that area, and should be organized to prevent mix-ups, cross-contamination, and improper release of HCT/Ps.

Before the completion of the donor-eligibility determination, you must keep an HCT/P in quarantine and clearly identify it as in quarantine (§§ 1271.60(a) and (b)). The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution (§ 1271.60(b)). Quarantine means the 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 (§ 1271.3(q)). An example of automated designation is the use of a validated computer system to maintain information on bar-code-labeled HCT/Ps held in a freezer. When you release the HCT/P, the computer system is activated to ensure identification and retrieval of the specific HCT/P for the intended recipient.

B. How do I determine appropriate storage temperatures for my HCT/Ps?

Under § 1271.260(b), you must store HCT/Ps at an appropriate temperature. The storage temperature should be sufficient to prevent conditions that could increase the risk of contamination of each HCT/P stored, considering the types of packaging and preservatives used, and the expected duration of storage. There are voluntary standards for storage temperatures issued by professional organizations, and you could follow these established industry standards where the standards meet the requirements in this section. Alternatively, you could establish your own criteria for storage temperature(s) and storage period(s) for specific HCT/Ps stored in your facility. See Section IX.D of this guidance for further information about monitoring the range of temperatures.

C. How do I determine whether an expiration date must be assigned to my HCT/Ps?

Where appropriate, you must assign an expiration date to each HCT/P based on the following factors (§ 1271.260(c)):

- HCT/P type;
- processing, including the method of preservation;
- storage conditions; and
- packaging.

An expiration date based on the factors listed above would be considered appropriate for your HCT/P if the absence of a defined expiration date could reasonably be expected to result in the product not meeting its specified requirements related to prevention of the introduction, transmission, or spread of communicable diseases. We consider it appropriate to assign expiration dates for fresh (i.e., non-cryopreserved) HCT/Ps, and for

HCT/Ps that are thawed or reconstituted prior to administration. If such applicable expiration dates have been established by industry or medical practice and meet the requirements of this section, you may use those dates for your HCT/Ps, whether fresh or preserved. If scientific data do not exist for establishing expiration dates, then an expiration date may not be applicable.

Example: Where appropriate, you must assign expiration dates to final products, both fresh and cryopreserved, based on the listed factors in § 1271.260(c), as needed to ensure that they remain free from microbial contamination. It may not be necessary to assign expiration dates to HCT/Ps that are cryopreserved, because there is a low risk of contamination as long as they remain immersed in the liquid phase or retained in the vapor phase of liquid nitrogen in containers that maintain their integrity and barrier properties throughout the storage period.

D. What should I do when proper storage conditions are not met?

You must take and document corrective action whenever proper storage conditions are not met (§1271.260(d)). For example, in response to an alert from your temperature monitoring system indicating temperatures outside acceptable limits, you may need to transfer your HCT/Ps to an alternative storage area. If the temperature excursion was of sufficient duration to increase the risk of contamination, you may need to discard or otherwise dispose of the affected products. After taking the appropriate corrective action(s), you should document the transfer or other disposition of each affected product.

E. What temperature limits must I establish during manufacturing?

Under § 1271.260(e), you must establish acceptable temperature limits for storage of HCT/Ps at each step of the manufacturing process to inhibit the growth of infectious agents. You must maintain and record storage temperatures for HCT/Ps. You must periodically review recorded temperatures to ensure that temperatures have been within acceptable limits.

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

F. What procedures related to storage must I establish and maintain?

Section 1271.260(a) through (d) requirements are core CGTP requirements (§ 1271.150(b)(8)). Therefore, you must establish and maintain procedures in accordance with § 1271.180.

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

A. What should I do before accepting an HCT/P from another establishment?

Under § 1271.265(a), you must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. You must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission. When you receive an HCT/P, you should visually inspect the shipping carton, 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. Am I required to perform a microbiological culture of an HCT/P prior to processing the HCT/P?

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 is to culture the HCT/P prior to processing. This culture is known as the pre-processing 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, 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.

C. What is predistribution shipment?

Predistribution shipment is the conveyance or shipment of an HCT/P within your establishment or between establishments before it has met its release criteria (i.e., it is not available for distribution). The sender must determine and document whether the HCT/P has met pre-established criteria designed to prevent communicable disease transmission

before shipping it. The HCT/P must be kept in quarantine during pre-distribution shipment and upon receipt (see § 1271.265(a) and (b)).

Example 1: An HCT/P is being shipped from the recovery establishment to the processing establishment. The HCT/P should be transported in a shipping container that is capable of maintaining the desired temperature during transport and that is capable of withstanding physical stress.

Example 2: Predistribution shipment can also occur within one establishment (e.g., transported between buildings or transported between floors in the same building before the HCT/P is available for distribution). Transferring HCT/Ps from one room to the next during processing (between steps) is not considered predistribution shipping.

D. When is an HCT/P available for distribution?

Available for distribution means that the HCT/P has been determined to meet all release criteria (§ 1271.3(z)). Distribution means 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. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor (§ 1271.3(bb)).

For example, there are brokers who facilitate HCT/P distribution by identifying potential clients/consignees (whether within the United States or for export) in need of particular HCT/Ps. If these brokers only match up clients with HCT/P establishments and never take physical possession of the HCT/Ps, they would not be considered a distributor.

Note that these requirements also do not apply with respect to carriers, such as Federal Express, United Parcel Service, or the United States Postal Service, who are exempt from the regulations in this part as noted in § 1271.15(c).

E. What must I do before making an HCT/P available for distribution?

Before making an HCT/P available for distribution, you must review manufacturing records (such as records from the donor eligibility determination, recovery, processing, and storage) and tracking records pertaining to the HCT/P, and, on the basis of that record review, you must verify and document that the release criteria have been met (§ 1271.265(c)(1)).

You must not make available for distribution an HCT/P that:

- is in quarantine;
- is contaminated (note that skin cultures taken post-processing may be positive for non-pathogenic normal flora but this is not considered contamination);

- is from a donor who has been determined to be ineligible or a donor with an incomplete donor eligibility determination (except as provided in §§ 1271.60, 1271.65, and 1271.90); or
- otherwise does not meet release criteria designed to prevent communicable disease transmission. (§ 1271.265(c)(2)).

If the HCT/P establishment maintains records in more than one location, faxing or emailing records for review prior to release for distribution is acceptable provided that the records can be adequately evaluated (e.g., legible and accurate).

F. Who must determine that an HCT/P is available for distribution?

A responsible person must make this determination and document and date the determination that an HCT/P is available for distribution (§ 1271.265(c)(1)). A responsible person means a person who is authorized to perform designated functions for which he or she is trained and qualified (§ 1271.3(t)).

G. May I release an HCT/P if it has been manufactured under a departure from a procedure?

If you make a departure from a procedure (SOP deviation) that is relevant to preventing risks of communicable disease transmission, you must not make an HCT/P manufactured under the departure available for distribution unless a responsible person has determined that the departure does not increase the risk of communicable disease through the use of the HCT/P. You must record and justify any departure from a procedure at the time of its occurrence (§ 1271.265(c)(3)).

Example: 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)).

H. Does a distributor need to make an assessment that the HCT/P is available for distribution?

The establishment that determines that the HCT/P is available for distribution must comply with § 1271.265(c). This could be the distributor or the processing establishment, depending upon the arrangement between the two.

I. Am I required to validate or verify packaging and shipment of HCT/Ps?

Process validation or verification only applies to processing (§§ 1271.3(ff) and 1271.230(a)). Since packaging and shipping are not part of processing, they are not required to be validated or verified. The packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination (§ 1271.265(d)).

J. How do I determine appropriate shipping conditions?

For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit (§ 1271.265(d)). You could use industry standards, if available, or establish for yourself appropriate temperature and time limits during shipping. It is also important to ensure that appropriate conditions are maintained throughout distribution. If you have a contract, agreement or other arrangement with distributors, sub-distributors and/or sales agents who distribute, you should ensure that appropriate conditions will be maintained before entering into such contracts, agreements or other arrangements.

K. What procedures and documentation must I have for receipt, predistribution shipment, and distribution of an HCT/P?

Section 1271.265(a) through (d) requirements are core CGTP requirements (§ 1271.150(b)(9)). Therefore, you must establish and maintain procedures in accordance with § 1271.180. Under § 1271.265(e), you must establish and maintain procedures, including release criteria, for receipt, predistribution shipment, availability for distribution, and packaging and shipping. Documentation must include the following:

- identification of the HCT/P;
- identification of the sender (establishment that supplied the HCT/P);
- activities that you performed on the HCT/P (e.g., inspection, acceptance or rejection of the HCT/P) and the results of each activity;
- date(s) of activity;
- quantity of HCT/P subject to the activity (e.g., received or distributed); and
- disposition of the HCT/P (e.g., identity of the consignee to whom the HCT/P was sent). (§ 1271.265(e)(1) through (5)).

For example, you could accomplish this with a checklist or a packing list.

L. Is an establishment such as a hospital that only receives and stores HCTP/s required to register under § 1271.1(b)?

In accordance with § 1271.15(d), a hospital that only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within its facility, but does not recover, screen, test, process, label, package, or distribute HCT/Ps, is not required to register.

However, if a hospital sends the HCT/P to other establishments (e.g., other hospitals or ambulatory sites), the hospital is functioning as a distributor and is required under § 1271.1(b) to register and list its HCT/Ps.

M. Am I permitted to accept HCT/Ps that are returned to me and place the returned HCT/Ps back into inventory?

Under § 1271.265(f), you must establish and maintain procedures to determine if an HCT/P that is returned to your establishment is suitable to be returned to inventory. If return is not permitted, this should be made clear to the consignee. If return is permitted, you should specify the conditions under which the return could be accepted.

XIX. RECORDS (§ 1271.270)

A. What are the general requirements for records?

Under § 1271.270(a), you must maintain records concurrently with the performance of each step required in 21 CFR part 1271, subparts C and D. All required records must be accurate, indelible, and legible.

To help ensure the accuracy of records retained, we recommend that establishments that make an HCT/P available for distribution obtain records directly from the creator of such documents whenever possible (e.g., serology/microbiology results should be obtained directly from the testing laboratory; death certificates, if needed to make an adequate donor eligibility determination, should be obtained directly from the state health official). The records must identify the person performing the work and the dates of the various entries, and must be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular HCT/P involved (§ 1271.270(a)). For specific requirements for retention of donor eligibility records, see § 1271.55(d).

B. What kind of records management system must I have?

Under § 1271.270(b), you must establish and maintain a records management system relating to core CGTP requirements. Under this system, you must maintain records pertaining to a particular HCT/P in such a way as to facilitate review of the 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. You must also maintain and organize records pertinent to the manufacture of the HCT/P (e.g., labeling and packaging procedures, and equipment logs) under the records management system. If you maintain records in more than one location, you must design the records management system to ensure prompt identification, location, and retrieval of all records.

The regulations do not specify the details of a records management system. You should organize your records in a useful manner in accordance with the requirements in this section.

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 and cleaning records, to the processor. The recovery establishment must maintain copies of all transferred records and organize them in their records management system.

C. What are acceptable methods of record retention?

Under § 1271.270(c), you may maintain records electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Equipment that is necessary to make the records available and legible, such as computer and reader equipment, must be readily available. You must back up records stored in electronic systems.

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, 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.

D. For how long must I retain my HCT/P manufacturing records?

Under § 1271.270(d), you must retain all records for 10 years after their creation, unless stated otherwise in 21 CFR part 1271. However, you must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest. You must retain records for archived specimens of dura mater for 10 years after the appropriate disposition of the specimens.

Example 1: Laboratories that perform communicable disease testing of donor specimens and/or microbiological testing of HCT/Ps would not know the date of administration, distribution, disposition, or expiration. These laboratories would be required to keep donor testing information for 10 years after the creation of the record.

Example 2: A cord blood establishment goes out of business, and transfers the remaining products in inventory to another cord blood establishment. All of the original

manufacturing records for these products should be transferred to the establishment storing the cord blood and kept for at least 10 years after the HCT/P is administered.

E. What records of contracts and agreements must I maintain?

Under § 1271.270(e), you must maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for you (see § 1271.150(c)(1)). You must have this information available during an inspection conducted under § 1271.400. We recommend that contracts, agreements or other arrangements describe the responsibilities of all parties. For instance, a contract, agreement or other arrangement with an individual or establishment who obtains the donor's hospital records should describe the information that you want that individual or establishment to obtain.

For example, when donor eligibility is determined following a review of records obtained by another establishment, the contract, agreement or other arrangement might specifically identify what records will be obtained, in what format they will be provided, responsibilities for record retention and access, and if the reviewing firm will convey donor eligibility conclusions back to the firm that collected the information.

XX. TRACKING (§ 1271.290)

Under § 1271.290(a), if you perform any step in the manufacture of an HCT/P in which you handle the HCT/P, you must track each such HCT/P. You must perform tracking in accordance with 21 CFR part 1271, to facilitate the investigation of an actual or suspected transmission of a communicable disease and to take appropriate and timely corrective action. If you do not handle the HCT/P (e.g., you are the testing laboratory that receives a blood specimen, but you do not actually handle the HCT/P), you do not have to participate in the tracking requirements.

A. How extensive a tracking system must I establish and maintain?

You must have a tracking system in place that enables the HCT/P to be tracked from the donor to the receiving facility (consignee) or final disposition and back to the donor (§ 1271.290(b)(1)). 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, 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 cannot include any protected health information, such as the donor's name, social security number or medical record number (with some exceptions as noted below). You may adopt the distinct identification code assigned by another establishment engaged in manufacturing, or assign a new code, but you should verify and/or validate that your tracking system is effective. The distinct identification code must be able to be related to the donor, (see § 1271.290(c)) but does not necessarily have to be on all records concerning the donor or on the package insert. However, the distinct identification code must be affixed to the HCT/P container (§ 1271.370(b)(1)).

As described in § 1271.290(c), the HCT/P establishment cannot assign an individual's name, social security number, or hospital medical record number as the HCT/P distinct identification code. However, these are acceptable for use in the case of autologous, directed reproductive, or first-degree or second-degree blood relative donations (§ 1271.55(a)(1)).

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 (§ 1271.290(d)). In addition, as part of your tracking system, you must establish and maintain a method for documenting the disposition of each of your HCT/Ps, to enable tracking from the donor to the consignee or final disposition. This information must permit the prompt identification of the consignee of the HCT/P, if any (§ 1271.290(e)).

Under § 1271.290(f), at or before the time of distribution of an HCT/P to a consignee, you must inform the consignee in writing of the requirements in § 1271.290 and of the tracking system that you have established and are maintaining to comply with these requirements. As part of the tracking system requirements, you should inform the consignee that the consignee should record a distinct identification code in a record and in the patient's file, and that the consignee should complete and return HCT/P disposition information according to the established instructions. 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. You might also enhance consignee feedback by providing your consignee with labels that identify each product and the establishment that provided it, and tracking logs for the hospitals to use to control inventory.

D. Are there specific requirements for dura mater donors?

Under § 1271.290(g), you must archive appropriate specimens from each donor of dura mater, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of TSE, and to enable appropriate disposition of any affected non-administered dura mater tissue, if necessary. We recommend in "Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Human Dura Mater" (Ref. 8), that specimens be retained 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.

XXI. COMPLAINT FILE (§ 1271.320)

Under § 1271.320(a), you must establish and maintain procedures for the review, evaluation, and documentation of complaints relating to core CGTP requirements, and the investigation of complaints as appropriate. A complaint (§ 1271.3(aa)) is 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.

A. What information about each complaint must I have in my complaint file?

Under § 1271.320(b), you must maintain a record of complaints that you receive in a file designated for complaints. The complaint file must contain sufficient information about each complaint for proper review and evaluation of the complaint (including the distinct identification code of the HCT/P that is the subject of the complaint) and for determining whether the complaint is an isolated event or represents a trend. You must make the complaint file available for review and copying upon request from FDA. We may make requests for review of complaint files by telephone, fax, mail, or in person. When copying complaint files, we will take steps to protect the identity of the donor and/or recipient.

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. An event that must be reported to FDA as described in § 1271.350

(e.g., an adverse reaction related to communicable disease transmission), must be reviewed, evaluated, and investigated as soon as practical.

For complaints relating to core CGTP requirements that are not required to be reported, you must still perform a review and evaluation to determine whether an investigation is necessary. An investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, you must maintain a record that includes the reason no investigation was made, and the name of the individual(s) responsible for the decision not to investigate (§ 1271.320(c)).

XXII. REPORTING (§ 1271.350)

Under § 1271.330, the § 1271.350 reporting requirements apply only for nonreproductive HCT/Ps described in § 1271.10 regulated solely under section 361 of the PHS Act. HCT/Ps that are drugs or devices regulated under the Act, or are biological products regulated under section 351 of the PHS Act, are not subject to these reporting requirements.

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)). Under § 1271.350(a), you must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. In addition, you must report to FDA an adverse reaction involving a communicable disease if it:

- is fatal;
- is life-threatening;
- results in permanent impairment of a body function or permanent damage to body structure; or
- necessitates medical or surgical intervention, including hospitalization.

If the adverse reaction does not involve a communicable disease transmission (e.g., primary graft failure after corneal transplantation, hemolysis due to an ABO-incompatibility in a patient who has received hematopoietic stem/progenitor cells), you do not have to report to FDA such an adverse reaction.

Example 1: A patient has surgery on his knee following an injury, and receives a patellar tendon. Several days after the surgery, the patient develops severe pain in the knee. He is taken back to the operating room, where his knee is examined. Purulent fluid is removed. This fluid is cultured and grows Methicillin resistant Staphylococcus aureus (MRSA). The surgeon contacts the HCT/P establishment. The medical director reviews the donor's records and the manufacturing records for the tendon. The pre-processing cultures were positive for MRSA, but the post-processing cultures were negative. The

validation studies for the antibiotic soaking process are reviewed and seem to be in order. You must report this adverse reaction, even though the post-processing cultures were negative, because there is a reasonable possibility that the HCT/P caused the response, the adverse reaction involves a communicable disease, and it necessitated medical intervention.

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.

Example 3: A patient spikes a fever and develops shaking chills 45 minutes after infusion of autologous peripheral blood stem cells. The patient had already received antibiotics for two days prior to the infusion for febrile neutropenia following high dose chemotherapy, but had no fever at the start of the infusion. The treating physician determines that the febrile reaction is not related to the HCT/P and the patient's antibiotic regimen is not modified. You would not be required to report this adverse reaction because no additional intervention was necessary and there is not a reasonable possibility that the HCT/P caused the response.

B. What is considered a medical or surgical intervention that I must report to FDA?

For the purpose of § 1271.350(a)(1)(iv), a medical or surgical intervention is an action, outside the bounds of the medical treatment normally given after administration of an HCT/P, which is intended to treat known or suspected transmission of communicable disease or infection affecting the patient. Following a thorough review, the establishment that made the HCT/P available for distribution should decide the following:

- if the adverse reaction involves a communicable disease; and
- whether or not there is a reasonable possibility that the adverse reaction is related to the HCT/P.

Example 1. Medical intervention would include prescribing, increasing the dose of, or changing an antibiotic outside the bounds of normal post-operative treatment for treatment of a known or suspected infection.

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.

Example 3. Surgical intervention would include returning a patient to the operating room or performing an incision and drainage procedure in the clinic for treatment of a known or suspected infection, or its consequences.

C. How do I report adverse reactions to FDA?

You must submit to FDA each report of an adverse reaction on a Form FDA 3500A within 15 calendar days of initial receipt of the information (§ 1271.350(a)(2)). You can find additional information about how to report adverse reactions in the "Guidance for Industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 2). This guidance provides supplemental instructions for reporting using the MedWatch Form FDA 3500A. You can find additional information on reporting on FDA's tissue webpage at http://www.fda.gov/cber/tiss.htm.

D. What kind of information should I review when investigating adverse reactions?

We recommend that you review the following information while investigating reports of adverse reactions:

- pre- and post-processing culture results;
- donor screening records;
- donor testing results;
- donor eligibility determination;
- donor identification code;
- lot number;
- receipt of complaints involving recipients of other HCT/Ps from the same donor; and
- the occurrence of any processing deviations from your established SOPs.

Examples of additional information you might review if obtainable:

- results of pre-implant cultures (collected by the implanting facility just prior to transplantation);
- date of implantation/explantation;
- symptoms of infection in the recipient and dates of onset;
- recipient's serologic or culture results;
- medical and surgical interventions required:
- pathology reports;
- recipient's risk factors if available;
- physician's impression about the cause of the infection; and
- recipient's clinical records.

E. When do I submit a followup report to FDA?

Under § 1271.350(a)(3), you must submit to FDA followup reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, you may be required to submit a followup report describing briefly the steps taken to seek additional information and the reasons why it could not be obtained.

F. What procedures did FDA develop to handle adverse reaction reports for HCT/Ps?

CBER formed a Tissue Safety Team to review and monitor adverse reaction reports and to investigate them as necessary. We developed standard operating procedures and policies (SOPP) to ensure that the responsibilities for addressing reported adverse reactions associated with HCT/Ps are clearly established. The SOPP 8508, "Procedures for Handling Adverse Reaction Reports Related to '361' Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 13), describes the procedures that CBER routinely follows when receiving and investigating adverse reaction reports associated with HCT/Ps.

G. How do I report an HCT/P deviation to FDA?

Under § 1271.350(b)(3), you must report each HCT/P deviation that relates to a core CGTP requirement on Form FDA 3486, available at http://www.fda.gov/cber/biodev/bpdrform.pdf, within 45 days of the discovery of the event. The form may be submitted either electronically at http://www.fda.gov/cber/biodev/biodevsub.htm or by mail to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

H. What are the general requirements for HCT/P deviation reporting?

Under § 1271.3(dd), an HCT/P deviation means an event:

- that represents a deviation from applicable regulations in 21 CFR part 1271 or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or
- that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

Under § 1271.350(b), you must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step (§ 1271.350(b)(1)). You must report any such HCT/P deviation relating to the core CGTP requirements if the HCT/P deviation occurred in your facility or in a facility that performed a manufacturing step for

you under contract, agreement, or other arrangement (§ 1271.350(b)(2)). Under § 1271.350(b)(2), each report must contain:

- a description of the HCT/P deviation;
- information relevant to the event and the manufacture of the HCT/P involved; and
- information on all follow-up actions that have been or will be taken in response to the HCT/P deviation (e.g., recalls).

XXIII. LABELING (§ 1271.370)

Under § 1271.330, the labeling requirements in § 1271.370 apply only for non-reproductive HCT/Ps described in § 1271.10 that are regulated solely under section 361 of the PHS Act. HCT/Ps that are drugs or devices regulated under the Act, or are biological products regulated under section 351 of the PHS Act, are not subject to these labeling requirements.

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. 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);
- description of the type of HCT/P;
- expiration date, if any; 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)). Note that the label can include the affixed container label or an attached tie-tag.

B. Is the manufacturer expected to place the distinct identification code on information that accompanies each distributed HCT/P?

Under § 1271.370(b)(1), the distinct identification code must be affixed to the HCT/P container, and assigned in accordance with § 1271.55(a)(1) and § 1271.290(c). There is no requirement that the distinct identification code appear on other information accompanying the HCT/P, such as the instructions for use described in § 1271.370(c). Additionally, there is no requirement to place the distinct identification code on the summary of records described in § 1271.55(b). However, your labeling procedures should be designed to ensure that consignees can readily link the product to all required labeling and accompanying records, such as instructions for use.

C. What additional information must appear on the HCT/P label or accompany the HCT/P?

Under § 1271.370(c), the following information must either appear on the HCT/P label or accompany the HCT/P:

- name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution;
- storage temperature;
- other warnings, where appropriate; and
- instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases.

D. How can I maintain privacy with regard to the warning statements?

If it is physically possible to include some or all of the warning statements on the HCT/P container label, but there are concerns about displaying private information (e.g., to family members or other visitors present in the patient's room while an HCT/P is being administered), it is acceptable to place the warning statements on the HCT/P container label or an attached tie-tag in a manner that limits visibility to visitors but allows clear display of the information to the healthcare providers administering the HCT/P.

E. Must the name and address of the processing establishment, if different from the establishment that determines that the HCT/P meets release criteria and makes it available for distribution, be included on the label or other accompanying information provided to the consignee?

You are not required to include the names of all establishments that performed manufacturing steps in the labeling. Under § 1271.370(c)(1), only the name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution must appear on the HCT/P label or accompany the HCT/P. Note that the name and address of the establishment that made the donor-eligibility determination must appear in the summary of records that accompanies the HCT/P (§ 1271.55(b)).

However, if the establishment that makes the donor-eligibility determination is not the same establishment that makes the HCT/P available for distribution, the labeling or accompanying information should contain the name and address of both establishments and specify which establishment performed which function.

XXIV. REFERENCES

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3. FDA Manual of Standard Operating Procedures and Policies: Regulatory - Cellular, Tissue and Gene Therapies: Procedures for Handling Requests for Exemptions and Alternative Procedures for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Under 21 CFR Section 1271.155, SOPP 9151, June, 13, 2006 (http://www.fda.gov/cber/regsopp/regsopp.htm).

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