

THE COMPLETE FDA 1271

AMERICAN REGULATIONS FOR HUMAN

REPRODUCTIVE TISSUE BANKS

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(THE "INTERIM FINAL RULE" OF 24 MAY 2005)

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Introduction

On 25 May 2005 the US Food and Drug Administration will for the first time begin regulating human reproductive tissue banks that serve American physicians and their patients. These regulations are officially Part 1271 of title 21 of the Code of Federal Regulations (21 CFR Part 1271): Human Cellular and Tissue-Based Products or “HCT/Ps.” All of the actual regulations have been officially published in several issues of the *Federal Register*. For the convenience of the clients of Xytex Corporation, the various regulatory documents, called subparts, are collated here, verbatim. Since the government in each subsequent publication added and revised materials to previous subparts, the reader of the original publications must frequently refer from subpart to subpart; there is loss of continuity. It is the objective of this compilation by Xytex to bring each sentence written by the government into the intended sequence indicated by the government.

Part 1271 of 21 CFR is authorized by the Public Health Service (PHS) Act passed by the US Congress, specifically, its “section 361” which deals with communicable diseases, i.e. infectious diseases. Additional authorization comes from “section 351” of the Act, a section dealing with biological products. The provisions of 351 are more constraining than those of 361. A majority of establishments processing reproductive tissues and regulated by 21 CFR are affected only by section 361 of the PHS Act; but those doing more than minimal manipulation of the tissue must also conform to section 351 of the Act. The additional expectations of section 351 are beyond the scope of this document.

Several points in 1271 deserve emphasis. First is the importance of definitions. The government has defined and used words in ways that may seem unconventional and may even cause discomfort. For example, “tissue bank” is not a term used by the government; neither is “medical practice” or “program.” **Any** entity processing cells or tissues *ex vivo* for subsequent transfer to a person is defined by the government as an “establishment.” Tissue processing is called “manufacture.” *Manufacturing* entails many defined steps, the performance of any causes the entity to be defined as an establishment. Manufacturers, by definition, are establishments and most, but not all must be registered.

There are two parts to tissue manufacturing: one is the handling and evaluation of the tissue itself and the other is screening or testing of the donor of the tissue. “Manufacture includes, but it not limited to, any or all steps in the recovery, processing, storage, labeling, packaging or distribution of any human cell or tissue.” If an entity engages in any one component of donor evaluation or of handling the tissue itself, then the entity is a manufacturer and therefore is an establishment. Strictly speaking this includes donor recruitment agencies that screen donors and laboratories that test donors for sexually transmitted infections.

Establishments become subjected to 1271 if they minimally manipulate tissue OR if they manufacture tissue for homologous use. *Minimal manipulation* is any processes that does not alter relevant biological characteristics of cells and tissues. Although the government has not defined “relevant biological characteristics,” the context of these words suggest that they mean that the tissue continues to provide the physiological functions after minimal manipulation that were present prior to minimal manipulation. Some processes FDA specifically recognizes as minimal manipulations are soaking the cells or tissue in an antibiotic solution at a non-toxic concentration, culturing or centrifuging the cells and cryopreserving them. Clearly, IVF laboratories that work with gametes for transfer to anyone other than a sexually intimate partner of the donor are establishments that manufacture tissue and must be registered. *Homologous use* refers to the use of reproductive tissue in a recipient so that the tissue performs the same basic function in the recipient as it would in the donor.

Again, a few establishments in clinical reproductive medicine are exempted from almost all of 1271 including registration; but most are not. An establishment is exempted if it manufactures tissue only for “autologous use,” that is the transfer of cells back into the individual from whom the cells or tissue originally came during the same surgical procedure; this includes transfer to a sexually intimate partner. However, if the establishment has subjected the autologous tissue to “minimal manipulation” the establishment must comply with 1271; i.e. establishments doing minimal manipulation are NOT EXEMPT. But exemption is possible even then if the minimal manipulation has been performed by an independent (“outside”) establishment that is regulated by 1271. So if your practice contracts with a 1271 regulated establishment to manufacture tissue including steps involving minimal manipulation, even if that establishment is co-located within the premises of your practice, your practice may claim exemption from 1271

(regardless of whether it transfers autologous tissue or homologous). This exemption is predicated on the practice being a user of tissue, but not being involved in its manufacture. An entity that only receives or stores HCT/Ps solely for transfer in that facility is not required to register. (There are some other exemptions, none of which apply to a typical clinical reproductive medicine practice; these are designated in 1271.15.)

[If an establishment goes beyond minimal manipulation of the tissue, the establishment becomes subject to section 351 of the Public Health Services Act in addition to part 1271 of the CFR. Section 351 of the Act is far more limiting. Questions about whether a manufacturing step goes beyond minimal manipulation are first considered by the Tissue Reference Group (TRG), a committee in the Center for Biologics Evaluation and Research (CBER, pronounced “see-ber”) in the FDA. CBER has overall responsibility for implementing 1271. More information about the TRG can be found at www.fda.gov/cber/tissue/trg.htm.]

Part 1271 is organized into five subparts. Subpart A is entitled “General Provisions” and gives an overview of the purpose and scope of the Part. It also includes the definition of terms. Subpart B gives the “Procedures for Registration and Listing.” Any medical practice that is an “establishment” as defined in subpart A, unless specifically exempted, must register with the FDA and list the products being manufactured. Subparts C, D and E all concern current good tissue practices (cGTPs) which includes processes for selecting a donor and process for manufacturing the tissue. Specifically, subpart C deals with “Donor Eligibility;” subpart D, “Current Good Tissue Practice;” and subpart E, “Additional Requirements.” Interestingly, the FDA has exempted manufacturers of reproductive tissues from subparts D and E except to allow these establishments to request waivers from any specific provision of subpart C. This exemption from virtually all of subparts D and E will be revoked by the FDA should the exemption be found to increase the risk of members of the general populations to disease, especially infectious disease. Subpart F deals with “Inspection and Enforcement of Establishments.”

Part 1271 includes reproductive tissues, obviously, but it was not written exclusively for reproductive tissues. In fact, Part 1271 is a replacement for Part 1270 that was first put into place in 1993 to regulate other transplantable tissues including bone, cornea and skin. Part 1271 is comprehensive rather than special, so includes

many regulations not intended for reproductive tissues. This document includes the entire Part 1271; the reader must determine which parts are applicable to her or his practice.

In contrast to an accrediting agency such as the “Joint Commission,” American Association of Tissue Banks, College of American Pathologists or the International Organization for Standardization, the principle purpose of the FDA is to regulate, inspect and enforce, not to educate. Nevertheless, FDA promotes compliance; entrapment is not part of its mission. The FDA goes to great lengths to instruct personnel of regulated establishments about the FDA’s expectations of those establishments. The FDA solicits comments on proposed rules, and responds to those comments. They send speakers to address groups of affected persons and post notes of these meetings on the FDA’s Web site (www.fda.gov/cber/tissue/tisreg.gov). Furthermore, the FDA is famous for its “Guidance” documents and “Points to Consider”. Such material is also on the Web: www.fda.gov/cber/publications.htm and www.fda.gov/cber/tissue/docs.htm. Here they even explain their compliance programs. More detailed information about compliance is found at www.fda.gov/ora/compliance_ref/default.htm and at www.fda.gov/ora/cpgm/default.htm which gives the procedure an investigator is to follow while inspecting a tissue establishment.

As previously stated, the body of this booklet is a verbatim copy of Part 1271 arranged in numerical sequence provided by FDA. Also, a left margin has been created for notes from Xytex regarding the FDA text and editorial actions taken by Xytex. The FDA text speaks for itself; it is in plain English. Xytex has taken the liberty to editorialize, as you have seen in this “Introduction.” The comments of Xytex are the private views and interpretations of Xytex and are shared with its clients. The comments are not intended as legal advice and should not be used as such. Only a lawyer can provide you with legal advice. But Xytex did want its clients to be privy to corporate understanding of the FDA document.

Xytex acknowledges the possibility of inaccuracies in the transposition of the FDA documents. This serves as a **WARNING** to the reader and also as an invitation to bring any such mistakes to the attention of Xytex for any future revision.

Title (as revised
17 June 04)

Part 1271 –Human Cells, Tissues and Cellular Tissue-Based Products

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Title of Subpart C
slightly altered
by Xytex

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FDA's Final Rule speaks of "donor eligibility" rather than "donor suitability" used in proposed regulations.

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Authority (as revised on 10 March 04)

Authority: 42 U.S.C. 216, 243, 263a, 264, 271

SUBPART A – GENERAL PROVISIONS

1271.1 What are the purpose and scope of this part?

Purpose and Scope (as revised 10 March 04)

- (a) *Purpose.* The purpose of this part, in conjunction with 207.20(f), 210.1(c), 210.2, 807.20(e), and 820.1(a) of this chapter, is to establish procedures to prevent the introduction, transmission, and spread of communicable diseases and to create a unified registration and product listing system for establishments that manufacture human cellular and tissue-based products.
- (b) *Scope.* Manufacturers of human cellular and tissue-based products regulated solely under the authority of section 361 of the Public Health Service Act (the PHS Act) are required by this part to register and list their products with the Food and Drug Administration’s (FDA’s) Center for Biologics Evaluation and Research, and to comply with the other requirements contained in this part. Under 207.20(f) and 807.20(e), manufacturers of human cellular and tissue-based products regulated under

Xytex has alpha-betized these definitions. The original location is indicated in the margin.

section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act (the act) are required to register and list their products following the procedures in subpart B of this part; under 210.1(c), 210.2, 211.1(b), and 820.1(a), manufacturers of those products are required to comply with the donor-suitability procedures in subpart C of this part and current good tissue practice procedures in subpart D of this part in addition to all other applicable regulations.

1271.3 How does FDA define important terms in this part?

1271.3(v) or (ee)

Act means the Federal Food, Drug and Cosmetic Act.

1271.3(y)

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(a)

Autologous use means the implantation, transplantation, infusion or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.

Note in 1271.90 that “reproductive cells or tissues donated by a sexually intimate partner of the recipient for reproductive use” are similar to *autologous use*.

Sometimes the FDA has given more than one definition, each one is very similar. Only one version is given here

Available for distribution means that the HCT/P has been determined to meet all release criteria.

1271.3(x)

Biohazard legend appears on the label as follows and is used to mark HCT/Ps that present a known or suspected relevant communicable disease risk.

1271.3(h)



1271.3(i)

Blood component means a product containing a part of human blood separated by physical or mechanical means.

1271.3(j)

Colloid means:

- (1) A protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or
- (2) Blood components such as plasma and platelets.

1271.3(aa)

Complaint means any written, oral or electronic communication about a distributed HCT/P that alleges:

- (1) That a HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P;
- (2) Any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with current good tissue practice.

1271.3(k)

Crystalloid means an isotonic salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer’s lactate solution, or 5 percent dextrose in water.

1271.3(l)	<p><i>Directed reproductive donor</i> means a donor of reproductive cells or tissue (including semen, oocytes, and embryos to which the donor contributed the spermatozoa or oocyte) to a specific recipient, and who knows and is known by the recipient before donation. The term directed reproductive donor does not include a sexually intimate partner under 1271.90.</p>
<p>“Knows” and “Known” are not defined by the FDA</p>	
1271.3(bb)	<p><i>Distribution</i> 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.</p>
1271.3(m)	<p><i>Donor</i> means a person, living or dead, who is the source of cells or tissue for an HCT/P.</p>
1271.3(n)	<p><i>Donor medical history interview</i> means a documented dialogue about the donor’s medical history and relevant social behavior, including activities, behaviors and descriptions considered to increase the donor’s relevant communicable disease risk:</p> <ol style="list-style-type: none"> (1) With the donor, if the donor is living and able to participate in the interview, or (2) If not, with an individual or individuals able to provide the information sought in the interview (e.g., the donor’s next-of-kin, the nearest available relative, a member of the donor’s household, an individual with an affinity relationship, and/or the primary treating physician).
1271.3(cc)	<p><i>Establish and maintain</i> means define, document (in writing or electronically), and implement; then follow, review and as needed, revise on an ongoing basis.</p>
1271.3(b)	<p><i>Establishment</i> means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues and cellular and tissue-based products. “Establishment” includes:</p> <ol style="list-style-type: none"> (1) Any individual, partnership, corporation, association or other legal entity engaged in the manufacture of human cells, tissues and cellular and tissue-based products; and (2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products.
1271.3(x)	<p><i>FDA</i> means the Food and Drug Administration</p>
1271.3(dd)	<p><i>HCT/P deviation</i> means an event:</p> <ol style="list-style-type: none"> (1) That represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or

- (2) 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.

1271.3(c)

Homologous use means the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

1271.3(d)
Revised
18 Nov 04

Human cells, tissues or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to bone ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on synthetic matrix, and semen or other reproductive tissues. The following products are not considered HCT/Ps:

- (1) Vascularized human organs for transplantation;
- (2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;
- (3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered a HCT/P;
- (4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids or a sterilizing, preserving or storage agent, if the addition of that agent does not raise new clinical safety concerns with respect to the bone marrow);
- (5) Ancillary products used in the manufacture of HCT/P;
- (6) Cells, tissues and organs derived from animals other than humans; and
- (7) In vitro diagnostic products as defined in 809.3(a) of this chapter.

1271.3(ee)
and (pp)

Importer of Record means the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

1271.3(e)

Manufacture 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 the cell or tissue donor.

As noted below, *screening* and *testing* are not defined but the text of 1271 makes clear that these terms relate to *relevant communicable disease agents or diseases*.

Note that "relevant characteristics" and "relevant biological characteristics" are not defined.

Minimal manipulation means:

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

1271.3(f)

1271.3(w)

PHS Act means the Public Health Service Act

1271.3(o)

Physical assessment of a cadaveric donor means a limited autopsy or recent antemortem or postmortem physical examination of the donor to assess for signs of a relevant communicable disease and for signs suggestive of any risk factor for a relevant communicable disease.

1271.3(p)

Plasma dilution means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids.

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.

1271.3(gg)

Quality audit means a document, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

1271.3(hh) and (kk)

Quality program means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with this part. 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.

1271.3(q)

Quarantine means the storage or identification of an HCT/P, to prevent improper release, in a physically separated area clearly identified for such use, or through use of other procedures, such as automated designation.

1271.3(gg) and (ii)

Recovery means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion or transfer.

Relevant biological characteristics is not defined by FDA.

1271.3(r)

Note that the FDA does not define "communicable disease," nevertheless, it seems obvious that the term is limited to infectious diseases and does not include genetic diseases.

Other relevant communicable diseases identified by FDA are West Nile Virus (WNV), sepsis, vaccinia and severe acute respiratory syndrome (SARS). FDA requires donors to be tested for anticytomegalovirus (IgG & IgM). Physicians using donor gametes must have an SOP that describes the use of gametes from a CMV-positive donor. (See 1271.85(b)(2).)

Relevant communicable disease agent or disease [RCDAD] means:

- (1)(i) For all human cells and tissues, a communicable disease or disease agent listed as follows:
 - (a) Human immunodeficiency virus, types 1 and 2;
 - (b) Hepatitis B virus;
 - (c) Hepatitis C virus;
 - (d) Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease; and
 - (e) *Treponema pallidum*
- (ii) For viable, leukocyte-rich cells and tissues, a cell-associated disease agent or disease listed as follows:
 - (a) Human T-lymphotropic virus, type I; and
 - (b) Human T-lymphotropic virus, type II.
- (iii) For reproductive cells or tissues, a disease agent or disease of the genitourinary tract listed as follows:
 - (a) *Chlamydia trachomatis*; and
 - (b) *Neisseria gonorrhoea*.

(2)

A disease agent or disease not listed in paragraph (1) of this [definition].

- (i) For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with it, such as medical personnel, because the disease agent or disease:
 - (a) Is potentially transmissible by an HCT/P and
 - (b) Either of the following applies:
 - (1) The disease agent or disease has sufficient incidence and/or prevalence to affect the potential donor population, or
 - (2) The disease agent or disease may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.
- (ii) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and
- (iii) For which appropriate screening measure have been developed and/or an appropriate screening test for donor specimens has been licensed, approved or cleared for such use by FDA and is available.

1271.3(s)

Relevant medical records means a collection of documents that includes a current donor medical history interview; a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and, if available, the following:

- (1) Laboratory test results (other than results of testing for relevant communicable disease agents required under this subpart);
- (2) Medical records;
- (3) Coroner and autopsy reports; and
- (4) Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms or relevant communicable disease, and treatments related to medical conditions suggestive or risk for relevant communicable disease.)

Reproductive cells or tissues are not defined by the FDA. But see definitions of HCT/P, gamete and embryo.

1271.3(t)

Responsible person means a person who is authorized to perform designated functions for which he or she is trained and qualified.

1271.3(hh), (ij) and (mm)

Storage means holding HCT/Ps for future processing and/or distribution.

Screening is not defined here but is described in 1271.75 as a review of the donor's "relevant medical records."

Sexually intimate partner is not defined by the FDA.

Testing is not defined here but is described in 1271.80 and 1271.85.

1271.3(g)

Transfer means the placement of human reproductive cells or tissues into a human recipient.

1271.3(u) and (z)

Urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P.

1271.3(ii), (kk) and (nn)

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(jj), (ll) and (oo)

Viable leukocyte-rich cells or tissues is not defined here.

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

1271.10

Addendum from
10 March 04

Are my HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

- (a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:
- (1) The HCT/P is minimally manipulated;
 - (2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
 - (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids or a sterilizing, preserving or storage agent, provided that the addition of water, crystalloids or the sterilizing, preserve or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
 - (4) Either:
 - (i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
 - (ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 - (a) Is for autologous use;
 - (b) Is for allogeneic use in a first-degree for second-degree blood relative; or
 - (c) Is for reproductive use.
- (b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:
- (1) You must register with FDA;
 - (2) You must submit to FDA a list of each HCT/P manufactured; and
 - (3) You must comply with the other requirements contained in this part.

The owner or operator of an establishment, foreign or domestic, that manufactures a human cellular or tissue-based product, whether or not the product enters into interstate commerce, is required under this part to register with FDA, to submit to the agency a list of each human cellular or tissue-based product manufactured, and to comply with the other requirements of this part, if the product:

- (a) Is minimally manipulated;
- (b) Is not promoted or labeled for any use other than a homologous use;
- (c) Is not combined with or modified by the addition of any component that is a drug or a device; and
- (d)
 - (1) Either does not have a systemic effect; or
 - (2) Has a systemic effect, and –
 - (i) Is for autologous use;
 - (ii) Is for a family-related allogeneic use; or
 - (iii) Is for reproductive use.

1271.15 Are there any exceptions from the requirements of this part?

- (a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/Ps solely for non-clinical scientific or educational purposes.
- (b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure.
- (c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries or delivers HCT/Ps in the usual course of business as a carrier.
- (d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within your facility.
- (e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.
- (f) You are not required to register to list your HCT/Ps independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.

Criteria for regulation of human cellular and tissue-based products under the act and/or section 351 of the PHS Act.

Addendum
from 10
March 04

Human cellular or tissue-based products that are regulated as drugs, devices and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are subject to all applicable regulations in title 21, chapter 1. In conjunction with those regulations, the procedures in part 1271, subparts B, C and D shall be followed, as specified in 207.20(f), 210.1(c), 210.2, 211.1(b), 807.20(e), and 820.1(a) of this chapter. A human cellular or tissue-based product is regulated under the act and/or section 351 of the PHS Act if it:

- (a) Is more than minimally manipulated;
- (b) Is promoted or labeled for any use other than a homologous use;
- (c) Is combined with or modified by the addition of any component that is drug or a device; or
- (d) Has a systemic effect and –
 - (1) Is not for autologous use;
 - (2) Is not for a family-related allogeneic use; and
 - (3) Is not for reproductive use.

1271.20 If my HCT/Ps do not meet the criteria in 1271.10, and I do not qualify for any of the exceptions in 1271.15, what regulations apply?

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The following establishments are not required to register, list or meet the other requirements of this part:

- (a) Establishments that use human cellular or tissue-based products solely for non-clinical scientific or educational purposes;
- (b) Establishments that remove human cellular or tissue-based products from an individual and implant such cells or tissues into the same individual during the same surgical procedure;
- (c) Carriers who accept, receive, carry, hold or deliver human cellular or tissue-based products in the usual course of business as carriers;
- (d) Establishments that do not recover, screen, test, process, label, package, or distribute, but only receive or store human cellular or tissue-based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility.

SUBPART B – PROCEDURES FOR REGISTRATION AND LISTING

1271.21 When do I register, submit an HCT/P list, and submit updates?

- (a) You must register and submit a list of every HCT/P that your establishment manufactures within five days after beginning operations or within 30 days of the effective date of this regulation, whichever is later.
- (b) You must update your establishment registration annually in December, except as required by 1271.26. You may accomplish your annual registration in conjunction with updating your HCT/P list under paragraph (c) of this section.
- (c)
 - (i) If no change described in 1271.25(c) has occurred since you previously submitted an HCT/P list, you are not required to update your listing.
 - (ii) If a change described in 1271.25(c) has occurred, you must update your HCT/P listing with the new information:
 - (a) At the time of the change, or
 - (b) Each June or December, whichever month occurs first after the change.

1271.22 How and where do I register and submit an HCT/P list?

- (a) You must use Form FDA 3356 for:
 - (i) Establishment registration,
 - (ii) HCT/P listings, and
 - (iii) Updates of registration and HCT/P listing.
- (b) You may obtain Form FDA 3356:
 - (i) By writing to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator
 - (ii) By contacting any Food and Drug Administration district office;

- (iii) By calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800;
- (iv) By connecting to <http://www.fda.gov/opacom/morechoices/fdaforms/cber.html> on the Internet.
- (c)
 - (i) You may submit Form FDA 3356 to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator; or
 - (ii) You may submit Form FDA 3356 electronically through a secure Web server at <http://www.fda.gov/cber/tissue/tisreg.html>.

1271.25 What information is required for establishment registration and HCT/P listing?

- (a) Your establishment registration Form FDA 3356 must include:
 - (1) The legal name(s) of the establishment;
 - (2) Each location, including the street address of the establishment and the postal service ZIP code;
 - (3) The name, address, and title of the reporting official; and
 - (4) A dated signature by the reporting official affirming that all information contained in the establishment registration and HCT/P listing form is true and accurate, to the best of his or her knowledge.
- (b) Your HCT/P listing must include all HCT/Ps (including the established name and the proprietary name) that you recover, process, store, label, package, distribute, or for which you perform donor screening or testing. You must also state whether each HCT/P meets the criteria set out in 1271.10
- (c) Your HCT/P listing update must include:
 - (1) A list of each HCT/P that you have begun recovering, processing, storing, labeling, packaging, distributing, or for which you have begun donor screening or testing, that has not been included in any list previously submitted. You must provide all of the information required by 1271.25(b) for each new HCT/P.
 - (2) A list of each HCT/P formerly listed in accordance with 1271.21(a) for which you have discontinued recovery, processing, storage, labeling, packaging, distribution or donor screening or testing, including for each HCT/P so listed, the identity by established name and proprietary name, and the date of discontinuance. We request but do not require that you include the reason for discontinuance with this information.
 - (3) A list of each HCT/P for which a notice of discontinuance was submitted under paragraph (c)(2) of this section and for which you have resumed recover, processing, storage, labeling, packaging, distribution, or donor screening or testing, including the identity by established name and proprietary name, the date of resumption, and any other information required by 1271.25(b) not previously submitted.
 - (4) Any material change in any information previously submitted. Material changes include any change in information submitted on Form FDA 3356, such as whether the HCT/P meets the criteria set out in 1271.10.

1271.26 When must I amend my establishment registration?

If the ownership or location of your establishment changes, you must submit an amendment to registration within five days of the change.

1271.27 Will FDA assign me a registration number?

- (a) FDA will assign each location a permanent registration number.
- (b) FDA acceptance of an establishment registration and HCT/P listing form does not constitute a determination that an establishment is in compliance with the applicable rules and regulations or that the HCT/P is licensed or approved by FDA.

1271.37 Will establishment registrations and HCT/P listings be available for inspection, and how do I request information on registrations and listings?

- (a) A copy of the Form FDA 3356 filed by each establishment will be available for public inspection at the Office of Communication, Training and Manufacturers Assistance (HFM-48), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448. In addition, there will be available for inspection at each of the Food and Drug Administration district offices the same information for firms within the geographical area of such district office. Upon request and receipt of a self-addressed stamped envelope, verification of a registration number of the location of a registered establishment will be provided. The following information submitted under the HCT/P requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:
 - (1) A list of all HCT/Ps;
 - (2) A list of all HCT/Ps manufactured by each establishment;
 - (3) A list of all HCT/Ps discontinued; and
 - (4) All data or information that has already become a matter of public record.
- (b) You should direct your requests for information regarding HCT/P establishment registrations and HCT/P listings to the Office of Communication, Training and Manufacturers Assistance (HFM-48), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

Dated: January 2, 2001.

Jane E. Henney, *Commissioner of Food and Drugs*.

Donna E. Shalala, *Secretary of Health and Human Services*.

SUBPART C – DONOR ELIGIBILITY

1271.45 What requirements does this subpart contain?

- (a) *General*. This subpart sets out requirements for determining donor eligibility, including donor screening and testing. The requirements contained in this subpart are a component of current good tissue practice (CGTP) requirements. Other CGTP requirements are set out in subpart D of this part.

Note that Subpart C is part of CGTP. Subparts D and E also deal with CGTP, but establishments dealing solely with reproductive tissues are presently exempt from almost all of D and from all of E. (See 1271.150(c)(3) and 1271.330. There is no exemption from CGTP in Subpart C.

- (b) *Donor eligibility determination required.* A donor-eligibility determination, based on donor screening and testing for relevant communicable disease agents and diseases, is required for all donors of cells or tissue used in HCT/Ps, except as provided under 1271.90. In the case of an embryo or of cells derived from an embryo, a donor-eligibility determination is required for both the oocyte donor and the semen donor.
- (c) *Prohibition on use.* An HCT/P must not be implanted, transplanted, infused or transferred until the donor has been determined to be eligible, except as provided under 1271.60(d), 1271.65(b) and 1271.90 of this subpart.
- (d) *Applicability of requirements.* If you are an establishment that performs any function described in this subpart, you must comply with the requirements contained in this subpart that are applicable to that function.

1271.46 What procedures must I establish and maintain?

- (a) *General.* You must establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility and complying with all other requirements of this subpart. “Establish and maintain” means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis. You must design these procedures to ensure compliance with the requirements of this subpart.
- (b) *Review and approval.* Before implementation, a responsible person must review and approve all procedures.
- (c) *Availability.* Procedures must be readily available to the personnel in the area where the operations to which they relate are performed, or in a nearby area if such availability is impractical.
- (d) *Departures from procedures.* You must record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of its occurrence. You must not make available for distribution any HCT/P from a donor whose eligibility is determined under such a departure unless a responsible person has determined that the departure does not increase the risks of communicable disease transmission through the use of the HCT/P.
- (e) *Standard procedures.* You may adopt current standard procedures, such as those in a technical manual prepared by another organization, provided that you have verified that the procedures are consistent with and at least as stringent as the requirements of this part and appropriate for your operations.

1271.50 How do I determine if a donor is eligible?

- (a) *Determination based on screening and testing.* If you are the establishment responsible for making the donor-eligibility determination, you must determine whether a donor is eligible based upon the results of donor screening in accordance with 1271.75 and donor testing in accordance with 1271.80 and 1271.85. A responsible person as defined in 1271.3(t) must determine and document the eligibility of a cell or tissue donor.

- (b) *Eligible donor.* A donor is eligible under these provisions only if:
 - (1) Donor screening in accordance with 1271.75 indicates that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and disease and is free from communicable disease risks associated with xenotransplantation; and
 - (2) The results of donor testing for relevant communicable disease agents in accordance with 1271.80 and 1271.85 are negative or non-reactive, except as provided in 1271.80(d)(1).

1271.55 What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I maintain?

- (a) *Accompanying records.* Once a donor-eligibility determination has been made, the following must accompany the HCT/P at all times:
 - (1) A distinct identification code affixed to the HCT/P container, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P and, except in the case of autologous donations, directed reproductive donations, or donations made by first-degree or second-degree blood relatives, does not include an individual's name, social security number or medical record number;
 - (2) A statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and
 - (3) A summary of the records used to make the donor-eligibility determination.
- (b) *Summary of records.* The summary of records required by paragraph (a)(3) of this section must contain the following information:
 - (1) A statement that the communicable disease testing was performed by a laboratory:
 - (i) Certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.S. 263a) and 42 CFR part 493; or
 - (ii) That has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services in accordance with those provisions;
 - (2) A listing and interpretation of the results of all communicable disease tests performed;
 - (3) The name and address of the establishment that made the donor-eligibility determination; and
 - (4) In the case of an HCT/P from a donor who is ineligible based on screening and released under paragraph (b) of 1271.65, a statement noting the reason(s) for the determination of ineligibility.
- (c) *Deletion of personal information.* The accompanying records required by this section must not contain the donor's name or other personal information that might identify the donor.
- (d) *Record retention requirements.*
 - (1) You must maintain documentation of:

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- (i) Results and interpretation of all testing for relevant communicable disease agents in compliance with 1271.80 and 1271.85, as well as the name and address of the testing laboratory or laboratories;
 - (ii) Results and interpretation of all donor screening for communicable diseases in compliance with 1271.75; and
 - (iii) The donor-eligibility determination, including the name of the responsible person who made the determination and the date of the determination.
- (2) All records must be accurate, indelible and legible. Information on the identity and relevant medical records of the donor, as defined in 1271.3(s), must be in English or, if in another language, must be retained and translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.
 - (3) You must retain required records and make them available for authorized inspection by or upon request from FDA. Records that can be readily retrieved from another location by electronic means are considered “retained.”
 - (4) 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/Ps distribution, disposition or expiration, whichever is latest.

1271.60 What quarantine and other requirements apply before the donor-eligibility determination is complete?

- (a) *Quarantine.* You must keep an HCT/P in quarantine, as defined in 1271.3(q), until completion of the donor-eligibility determination required by 1271.50. You must quarantine semen from anonymous donors until the re-testing required under 1217.85(d) is complete.
- (b) *Identification of HCT/Ps in quarantine.* You must clearly identify as quarantined an HCT/P that is in quarantine pending completion of a donor-eligibility determination. The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution.
- (c) *Shipping of HCT/Ps in quarantine.* If you ship an HCT/P before completion of the donor-eligibility determination, you must keep it in quarantine during shipment. The HCT/P must be accompanied by records:
 - (1) Identifying the donor (e.g., by a distinct identification code affixed to the HCT/P container);
 - (2) Stating that the donor-eligibility determination has not been completed; and
 - (3) Stating that the product must not be implanted, transplanted, infused, or transferred until completion of the donor-eligibility determination, except under the terms of paragraph (d) of this section.
- (d) *Use in cases of urgent medical need.*
 - (1) This subpart C does not prohibit the implantation, transplantation, infusion or transfer of an HCT/P from a donor for whom the donor-

eligibility determination is not complete if there is a documented urgent medical need for the HCT/P, as defined in 1271.3(u).

- (2) If you make an HCT/P available for use under the provisions of paragraph (d)(1) of this section, you must prominently label it “NOT EVALUATED FOR INFECTIOUS SUBSTANCES,” and “WARNING: Advise patient of communicable disease risks.” The following information must accompany the HCT/P:
 - (i) The results of any donor screening required under 1271.75 that has been completed;
 - (ii) The results of any testing required under 1271.80 or 1271.85 that has been completed; and
 - (iii) A list of any screening or testing required under 1271.75, 1271.80 or 1271.85 that has not yet been completed.
- (3) If you are the establishment that manufactured an HCT/P used under the provisions of paragraph (d)(1) of this section, you must document that you notified the physician using the HCT/P that the testing and screening were not complete.
- (4) In the case of an HCT/P used for an urgent medical need under the provisions of paragraph (d)(1) of this section, you must complete the donor-eligibility determination during or after the use of the HCT/P, and you must inform the physician of the results of the determination.

1271.65 How do I store an HCT/P from a donor determined to be ineligible, and what uses of the HCT/P are not prohibited?

- (a) *Storage.* If you are the establishment that stores the HCT/P, you must store or identify HCT/Ps from donors who have been determined to be ineligible in a physically separate area clearly identified for such use, or follow other procedures, such as automated designation, that are adequate to prevent improper release until destruction or other disposition of the HCT/P in accordance with paragraph (b) or (c) of this section.
- (b) *Limited uses of HCT/P from ineligible donor.*
 - (1) An HCT/P from a donor who has been determined to be ineligible, based on the results of required testing and/or screening, is not prohibited by subpart C of this part from use for implantation, transplantation, infusion or transfer under the following circumstances:
 - (i) The HCT/P is for allogeneic use in a first-degree or second-degree blood relative;
 - (ii) The HCT/P consists of reproductive cells or tissue from a directed reproductive donor, as defined in 1271.3(l); or
 - (iii) There is a documented urgent medical need as defined in 1271.3(u).
 - (2) You must prominently label an HCT/P made available for use under the provisions of paragraph (b)(1) of this section with the Biohazard legend shown in 1271.3(h) with the statement “WARNING: Advise patient of communicable disease risks”, and in the case of reactive test results, “WARNING: Reactive test results for (name of disease agent or disease).” The HCT/P must be accompanied by the records required under 1271.55.

- (3) If you are the establishment that manufactured an HCT/P used under the provisions of paragraph (b)(1) of this section, you must document that you notified the physician using the HCT/P of the results of testing and screening.
- (c) *Non-clinical use.* You may make available for non-clinical purposes an HCT/P from a donor who has been determined to be ineligible, based on the results of required testing and/or screening, provided that it is labeled:
 - (1) “For Non-clinical Use Only” and
 - (2) With the Biohazard legend shown in 1271.3(h)

1271.75 How do I screen a donor?

- (a) *All donors.* Except as provided under 1271.90, if you are the establishment that performs donor screening, you must screen a donor of cells or tissue by reviewing the donor’s relevant medical records for:
 - (1) Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, including:
 - (i) Human immunodeficiency virus;
 - (ii) Hepatitis B virus;
 - (iii) Hepatitis C virus;
 - (iv) Human transmissible spongiform encephalopathies including Creutzfeld-Jakob disease
 - (v) *Treponema pallidum*; and
 - (2) Communicable disease risks associated with xenotransplantation.
- (b) *Donors of viable, leukocyte-rich cells or tissue.* In addition to the relevant communicable disease agents and diseases for which screening is required under paragraph (a) of this section, and except as provided under 1271.90, you must screen the donor of viable, leukocyte-rich cells or tissue by reviewing the donor’s relevant medical records for risk factors for and clinical evidence of relevant cell-associated communicable disease agents and diseases, including Human T-lymphotropic virus.
- (c) *Donors of reproductive cells or tissue.* In addition to the relevant communicable disease agents and disease for which screening is required under paragraphs (a) and (b) of this section, as applicable, and except as provided under 1271.90, you must screen the donor of reproductive cells or tissue by reviewing the donor’s relevant medical records for risk factors for and clinical evidence of infection due to relevant communicable diseases of the genitourinary tract. Such screening must include screening for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section. However, if the reproductive cells or tissues are recovered by a method that ensure freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then screening for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section is not required. Communicable disease agents of the genitourinary tract for which you must screen include:
 - (1) *Chlamydia trachomatis*; and
 - (2) *Neisseria gonorrhoea*
- (d) *Ineligible donors.* You must determine ineligible a donor who is identified as having either of the following:

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- (1) A risk factor for clinical evidence of any of the relevant communicable disease agents or diseases for which screening is required under paragraphs (a)(1)(i), (b), or (c) of this section; or
- (2) Any communicable disease risk associated with xenotransplantation.
- (e) *Abbreviated procedure for repeat donors.* If you have performed a complete donor screening procedure on a living donor within the previous six months, you may use an abbreviated donor screening procedure on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior.

1271.80 What are the general requirements for donor testing?

- (a) *Testing for relevant communicable diseases is required.* To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under 1271.90, if you are the establishment that performs donor testing, you must test a donor specimen for evidence of infection due to communicable disease agents in accordance with paragraph (c) of this section. You must test for those communicable disease agents specified in 1271.85. In the case of a donor one month of age or younger, you must test a specimen from the birth mother instead of a specimen from the donor.
- (b) *Timing of specimen collection.* You must collect the donor specimen for testing at the time of recovery of cells or tissue from the donor; or up to 7 days before or after recovery, except:
 - (1) For donors of peripheral blood stem/progenitor cells, bone marrow (if not excepted under 1271.3(d) (4)), or oocytes, you may collect the donor specimen for testing up to 30 days before recovery; or
 - (2) In the case of a repeat semen donor from whom a specimen has already been collected and tested, and for whom retesting is required under 1271.85 (d), you are not required to collect a donor specimen at the time of each donation.
- (c) *Tests.* You must test using appropriate FDA-licensed, approved or cleared donor screening tests, in accordance with the manufacture's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or disease; however, until such time as appropriate FDA-licensed, approved or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhoea* are available, you must use FDA-licensed, approved or cleared donor screening tests labeled for the detection of those organisms in an asymptotic, low-prevalence population. You must use a test specifically labeled for cadaveric specimens instead of a more generally labeled test when applicable and when available. Required testing under this section must be performed by a laboratory that either is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.
- (d) *Ineligible donors.* You must determine the following donors to be ineligible:
 - (1) A donor whose specimen tests reactive on a screening test for a communicable disease agent in accordance with 1271.85, except for a

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donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test;

- (2) (i) A donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected, unless:
 - (a) You test a specimen taken from the donor before transfusion or infusion and up to 7 days before recovery of cells or tissue; or
 - (b) You use an appropriate algorithm designed to evaluate volumes administered in the 48 hours before specimen collection, and the algorithm shows that plasma dilution sufficient to affect the results of communicable disease testing has not occurred.
- (ii) Clinical situations in which you must suspect plasma dilution sufficient to affect the results of communicable disease testing include but are not limited to the following:
 - (a) Blood loss is known or suspected in a donor over 12 years of age, and the donor has received a transfusion or infusion of any of the following, alone or in combination;
 - (1) More than 2,000 milliliters (mL) of blood (e.g. whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or
 - (2) More than 2,000 mL of crystalloids within one hour before death or specimen collection, whichever occurred earlier.
 - (b) Regardless of the presence or absence of blood loss, the donor is 12 years of age or younger and has received a transfusion or infusion of any amount of any of the following, alone or in combination:
 - (1) Blood (e.g. whole blood, red blood cells or colloids) within 48 hours before death or specimen collection, whichever occurred earlier, or
 - (2) crystalloids within one hour before death or specimen collection, whichever occurred earlier.

1271.85 What donor testing is required for different types of cells and tissues?

- (a) *All donors.* To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under 1271.90, you must test a specimen from the donor of cells or tissues, whether viable or non-viable for evidence of infection due to relevant communicable diseases including:
 - (1) Human immunodeficiency virus, type 1;
 - (2) Human immunodeficiency virus, type 2;
 - (3) Hepatitis B virus;
 - (4) Hepatitis C virus; and
 - (5) *Treponema pallidum*
- (b) *Donors of viable leukocyte-rich cells or tissue.* In addition to the relevant communicable disease agents for which testing is required under paragraph (a) of this section, and except as provided under 1271.90,
 - (1) You must test a specimen from the donor of viable, leukocyte-rich cells or tissue to adequately and appropriately reduce the risk of transmission of relevant cell-associated communicable disease, including
 - (a) Human T-lymphotropic virus, type I;

- (b) Human T-lymphotropic virus, type II; and
- (2) You must test a specimen from the donor of viable, leukocyte-rich cells or tissue for evidence of infection due to cytomegalovirus (CMV), to adequately and appropriately reduce the risk of transmission. You must establish and maintain a standard operating procedure governing the release of an HCT/P from a donor whose specimen tests reactive for CMV.

- (c) *Donors of reproductive cells or tissue.* In addition to the communicable disease agents for which testing is required under paragraphs (a) and (b) of this section, as applicable, and except as provided under 1271.90, you must test a specimen from the donor of reproductive cells or tissue to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents of the genitourinary tract. Such testing must include testing for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section. However, if the reproductive cells or tissues are recovered by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then testing for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section is not required. Communicable disease agents of the genitourinary tract for which you must test include:

- (1) *Chlamydia trachomatis*; and
- (2) *Neisseria gonorrhoea*;

- (d) *Re-testing anonymous semen donors.* Except as provided under 1271.90 and except for directed reproductive donors as defined in 1271.3(l), at least six months after the date of donation of semen from anonymous donors, you must collect a new specimen from the donor and test it for evidence of infection due to the communicable disease agents for which testing is required under paragraphs (a), (b) and (c) of this section.
- (e) *Dura mater.* For donors of dura mater, you must perform an adequate assessment designed to detect evidence of transmissible spongiform encephalopathy.

1271.90 Are there exceptions from the requirements of determining donor eligibility, and what labeling requirements apply?

- (a) *Donor eligibility determination not required.* You are not required to make a donor-suitability determination under 1271.50 or to perform donor screening or testing under 1271.75, 1271.80 and 1271.85 for:
 - (1) Cells and tissues for autologous use;
 - (2) Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or
 - (3) Cryopreserved cells or tissue for reproductive use, other than embryos originally exempt under paragraph (a)(1) or (a)(2) of this section at the time of donation, that are subsequently intended for directed donation, provided that
 - (i) Additional donations are unavailable, for example, due to infertility or health of a donor of the cryopreserved reproductive cells or tissue; and
 - (ii) Appropriate measures are taken to screen and test the donor(s) before transfer to the recipient.

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- (4) A cryopreserved embryo, originally exempt under paragraph (a)(2) of this section at the time of cryopreservation, that is subsequently intended for directed or anonymous donation. When possible, appropriate measures should be taken to screen and test the semen and oocyte donors before transfer of the embryo to the recipient.
- (b) *Required labeling.* As applicable, you must prominently label an HCT/P described in paragraph (a) of this section as follows:
- (1) “FOR AUTOLOGOUS USE ONLY,” if it is stored for autologous use.
 - (2) “NOT EVALUATED FOR INFECTIOUS SUBSTANCES,” unless you have performed all otherwise applicable screening and testing under 1271.75, 1271.80 and 1271.85. This paragraph does not apply to reproductive cells or tissue labeled in accordance with paragraph (b)(6) of this section.
 - (3) Unless the HCT/P is for autologous use only, “WARNING: Advise recipient of communicable disease risks,”
 - (i) When the donor-eligibility determination under 1271.50(a) is not performed or is not completed; or
 - (ii) If the results of any screening or testing performed indicate:
 - (A) The presence of relevant communicable disease agents and/or
 - (B) Risk factors for or clinical evidence of relevant communicable disease agents or diseases.
 - (4) With the Biohazard legend shown in 1271.3(h), if the results of any screening or testing performed indicate:
 - (i) The presence of relevant communicable disease agents and/or
 - (ii) Risk factors for or clinical evidence of relevant communicable disease agents or diseases.
 - (5) “Warning: Reactive test results for (name of disease agent or disease),” in the case of reactive test results.
 - (6) “Advise recipient that screening and testing of the donor(s) were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently,” for paragraphs (a)(3) or (a)(4) of this section.

Dated March 10, 2004

Lester M. Crawford, *Acting Commissioner for Food and Drugs*

Tommy G. Thompson, *Secretary of Health and Human Services*

SUBPART D – CURRENT GOOD TISSUE PRACTICE

1271.145 Prevention of the introduction, transmission, or spread of communicable diseases

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.

1271.150 Current good tissue practice requirements

- (a) *General.* This subpart D and subpart C of this part set forth current good tissue practice (CGTP) requirements. You must follow CGTP requirements to prevent the introduction, transmission, and spread of communicable disease through the use by HCT/Ps (by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing). Communicable diseases include, but are not limited to those transmitted by viruses, bacteria, fungi, parasites and transmissible spongiform encephalopathy agents. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging and distribution. The CGTP provisions specifically governing determinations of donor eligibility, including donor screening and testing, are set out separately in subpart C of this part.
- (b) *Core CGTP requirements.* The following are core CGTP requirements
- (1) Requirements relating to facilities in 1271.190(a) and (b);
 - (2) Requirements relating to environmental control in 1271.195(a);
 - (3) Requirements relating to equipment in 1271.200(a);
 - (4) Requirements relating to supplies and reagents in 1271.210(a) and (b);
 - (5) Requirements relating to recovery in 1271.215;
 - (6) Requirements relating to processing and process controls in 1271.220;
 - (7) Requirements relating to labeling controls in 1271.250 (a) and (b);
 - (8) Requirements relating to storage in 1271.260 (a) through (d);
 - (9) Requirements relating to receipt, pre-distribution shipment and distribution of an HCT/P in 1271.265(a) through (d); and
 - (10) Requirements relating to donor eligibility determinations, donor screening and donor testing in 1271.50, 1271.75, 1271.80 and 1271.85
- (c) *Compliance with applicable requirements.*
- (1) Manufacturing arrangements
 - (i) If you are an establishment that engages in only some operations subject to the regulations in this subpart and subpart C of this part, and not others, then you need only comply with those requirements applicable to the operations that you perform.
 - (ii) If you engage another establishment (e.g., a laboratory to perform communicable disease testing, or an irradiation facility to perform terminal sterilization), under a contract, agreement, or other arrangement, to perform any step in manufacture for you, that establishment is responsible for complying with requirements applicable to that manufacturing step.
 - (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. If, during the course of this contract, agreement or other arrangement, you become aware of information suggesting that the establishment may no longer be in compliance with such requirements, you must take reasonable steps to ensure the establishment complies with those requirements. If you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement or other arrangement with the establishment.

Note that Subpart C "Donor Eligibility" is part of Core CGTP

As stated in 1271.150(c)(3), regulations in Subparts D and E "are not being implemented for reproductive HCT/Ps." The CGTPs in these two Subparts describe good tissue processing practices and should be carefully considered before deciding against them. A court of law might believe that these CGTPs should be implemented by processors of reproductive tissues.

- (2) If you are the establishment that determines that an HCT/P meets all release criteria and makes 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 tacked in compliance with the requirements of this subpart and subpart C of this part and any other applicable requirements.
- (3) With the exception of 1271.150(c) and 1271.155 of this subpart, the regulations in this subpart are not being implemented for reproductive HCT/Ps described in 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, or for the establishments that manufacture them.
- (d) *Compliance with parts 210, 211 and 820 of this chapter.* With respect to HCT/Ps that are drugs (subject to review under an application submitted under section 505 of the Federal Food, Drug and Cosmetic Act or under a biological product license application under section 351 of the Public Health Service Act) or that are devices (subject to Premark review or notification under the device provision of the act or under a biological product license application under section 351 of the Public Health Service Act), the procedures contained in this subpart and in subpart C of this part and the current good manufacturing practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event that a regulation in part 1271 of this chapter is in conflict with a requirement in parts 210, 211 or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general.
- (e) *Where appropriate.* When a requirement is qualified by “where appropriate”, it is deemed to be “appropriate” unless you can document justification otherwise. A requirement is “appropriate” if non-implementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specific requirements related to prevention of introduction, transmission or spread of communicable disease agents and diseases, or in the establishment’s inability to carry out any necessary corrective action.

1271.155 Exemptions and alternatives

- (a) *General.* You may request an exemption or alternative from any requirement in subpart C or D of this part.
- (b) *Request for exemption or alternative.* Submit your request under this section to the Director of the appropriate Center (the Director), Center for Biologics Evaluation and Research or the Center for Devices and Radiological Health. The request must be accompanied by supporting documentation, including all relevant valid scientific data and must contain either:
 - (1) Information justifying the exemption from the requirement; or
 - (2) A description of a proposed alternative method of meeting the requirement.
- (c) *Criteria for granting exemption or alternative.* The Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of protecting the public health and/or preventing the introduction, transmission and spread of communicable diseases and that:
 - (1) The information submitted justifies an exemption; or

- (2) The proposed alternative satisfies that purpose of the requirement.
- (d) *Form of request.* You must ordinarily make your request for an exemption or alternative in writing (hard copy or electronically). However, if circumstances make it difficult (there is inadequate time) to submit your request in writing, you may make the request orally, and the Director may orally grant an exemption or alternative. You must follow your with an immediate written request to which the Director will respond in writing.
- (e) *Operation under exemption or alternative.* You must not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted. You may apply for an extension of an exemption or alternative beyond its expiration date, if any.
- (f) *Documentation.* If you operate under the terms of an exemption or alternative, you must maintain documentation of:
 - (1) FDA's granting of the exemption or alternative, and
 - (2) The date on which it began operating under the terms of the exemption or alternative.
- (g) *Issuance of an exemption or alternative by the Director.* In a public health emergency, the Director may issue an exemption from, or alternative to, any requirement in part 1271. The Director may issue an exemption or alternative under this section if the exemption or alternative is necessary to assure that certain HCT/Ps will be available in a specified location to respond to an unanticipated immediate need for those HCT/Ps.

1271.160 Establishment and maintenance of a quality program.

- (a) *General.* If you are an establishment that performs any step in the manufacture of HCT/Ps, you must establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable disease through the manufacture and use of HCT/Ps. The quality program must be appropriate for the specific HCT/Ps manufactured and the manufacturing steps performed. The quality program must address all core CGTP requirements listed in 1271.150(b).
- (b) *Functions.* Functions of the quality program must include:
 - (1) Establishing and maintaining appropriate procedures relating to core CGTP requirements, and ensuring compliance with the requirements of 1271.180 with respect to such procedures, including review, approval, revision;
 - (2) Ensuring that procedures exist for receiving, investigating, evaluating and documenting information relating to core CGTP requirements, including complaints, and for sharing 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:
 - (i) Other establishments that are known to have recovered HCT/Ps from the same donor;
 - (ii) Other establishments that are known to have performed manufacturing steps with respect to the same HCT/P; and
 - (iii) Relating to consignees, in the case of such information received after the HCT/P is made available for distribution, shipped to the

consignee, or administered to the recipient, procedures must include provision 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.

- (3) Ensuring that appropriate corrective actions relating to core CGTP requirements, including re-audits of deficiencies are taken and documented, as necessary. You must verify corrective actions to ensure that such actions are effective and are in compliance with CGTP. 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. Documentation of corrective actions must include, where appropriate:
 - (i) Identification of the HCT/P affected and a description of its disposition;
 - (ii) The nature of the problem requiring corrective action;
 - (iii) A description of the corrective action taken; and
 - (iv) The date(s) of the corrective action
 - (4) Ensuring the proper training and education of personnel involved in activities related to core CGTP requirements;
 - (5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);
 - (6) Investigating and documenting all product deviations and trends of HCT/P deviations relating to core CGTP requirements and making 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.
- (c) *Audits.* You must periodically perform for management review a quality audit, as defined in 1271.3(gg), of activities related to core CGTP requirements.
- (d) *Computers.* You must validate the performance of computer software for the intended use, and the performance of any changes to that software for the intended use, if you rely upon the software to comply with core CGTP requirements and if the software either is custom software or is commercially available software that has been customized or programmed (including software programmed to perform a user defined calculation or table) to perform a function related to core CGTP requirements. You must verify the performance of all other software for the intended use if you rely upon it to comply with core CGTP requirements. You must approve and document these activities and results before implementation.

1271.170.1 Personnel

- (a) *General.* You must have personnel sufficient to ensure compliance with the requirements of this part.
- (b) *Competent performance of functions.* You must have personnel with the necessary education, experience and training to ensure competent performance of their

assigned functions. Personnel must perform only those activities for which they are qualified and authorized.

- (c) *Training.* You must train all personnel, and re-train as necessary, to perform their assigned responsibilities adequately.

1271.180 Procedures

- (a) *General.* You must establish and maintain procedures appropriate to meet core CGTP requirements for all steps in the manufacture of HCT/Ps. You must design these procedures to prevent circumstances that increase the risk of the introduction, transmission and spread of communicable disease through the use of HCT/Ps.
- (b) *Review and approval.* Before implementation, a responsible person must review and approve these procedures.
- (c) *Availability.* These procedures must be readily available to the personnel in the area where the operations to which they relate are performed, or in a nearby area if such availability is impractical.
- (d) *Standard procedures.* If you adopt current standard procedures from another organization, you must verify that the procedures meet the requirements of this part and are appropriate for your operations.

1271.190 Facilities

- (a) *General.* 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-ups. 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 diseases
- (b) *Facility cleaning and sanitation*
 - (1) 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.
 - (2) You must dispose of sewage, trash and other refuse in a timely, safe, and sanitary manner.
- (c) *Operations.* 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.
- (d) *Procedures and records*
 - (1) You must 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.
 - (2) You must document and maintain records of, all cleaning and sanitation activities performed to prevent contamination of HCT/Ps. You must retain such records 3 years after their creation.

1271.195 Environmental control and monitoring

- (a) *General.* 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:
 - (1) Temperature and humidity controls;
 - (2) Ventilation and air filtration;
 - (3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
 - (4) Maintenance of equipment used to control conditions necessary for aseptic processing operations.
- (b) *Inspections.* 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) *Environmental monitoring.* 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.
- (d) *Records.* You must document, and maintain records of, environmental control and monitoring activities.

1271.200 Equipment

- (a) *General.* To prevent the introduction, transmission or spread of communicable diseases, 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. Any automated, mechanical, electronic or other equipment used for inspection, measuring or testing in accordance with this part must be capable of producing valid results. You must clean, sanitize and maintain equipment according to established schedules.
- (b) *Procedures and schedules.* 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.
- (c) *Calibration of equipment.* 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 in accordance with this part.
- (d) *Inspections.* You must routinely inspect equipment for cleanliness, sanitation and calibration, and to assure adherence to applicable equipment maintenance schedules.
- (e) *Records.* You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration and other activities performed in accordance with this section. 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.

1271.210 Supplies and reagents

- (a) *Verification.* 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 disease. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.
- (b) *Reagents.* Reagents used in processing and preservation of HCT/Ps must be sterile, where appropriate
- (c) *In-house reagents.* You must validate and/or verify the processes used for production of in-house reagents.
- (d) *Records.* You must maintain the following records pertaining to supplies and reagents:
 - (1) Records of the receipt of each supply or reagent, including the type, quantity, manufacturer, lot number, date of receipt and expiration date;
 - (2) Records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a certificate of analysis from the vendor; and
 - (3) Records of the lot of supply or reagent, used in the manufacture of each HCT/P.

1271.215 Recovery

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.

1271.220 Processing and Process Controls

- (a) *General.* 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.
- (b) *Pooling.* 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.
- (c) *In-process control and testing.* You must ensure that specified requirements, consistent with paragraph (a) of this section, 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 necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.
- (d) *Dura mater.*
 - (1) When there is a published validated process that reduces the risk of transmissible spongiform encephalopathy, you must use this process for

dura mater (or an equivalent process that you have validated), unless following this process adversely affect the clinical utility of the dura mater.

- (2) When you use a published validated process, you must verify such a process in your establishment.

1271.225 Process changes

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.

1271.230 Process validation

- (a) *General.* Where the results of a 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. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.
- (b) *Written representation.* 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.
- (c) *Changes.* When changes to a validated process subject to paragraph (a) of this section occur, you must review and evaluate the process and perform revalidation where appropriate. You must document these activities.

1271.250 Labeling controls

- (a) *General.* You must establish and maintain procedures to control the labeling of HCT/Ps. You must design these procedures to ensure proper HCT/P identification to prevent mix-ups.
- (b) *Verification.* Procedures must include verification of label accuracy, legibility and integrity.
- (c) *Labeling requirements.* Procedures must ensure that each HCT/P is labeled in accordance with all applicable labeling requirements, including those in 1271.55, 1271.60, 1271.65, 1271.90 and 1271.370, and that each HCT/P made available for distribution is accompanied by documentation of the donor eligibility determination as required under 1271.55.

1271.260 Storage

- (a) *Control of storage areas.* You must control your storage areas and stock rooms to prevent:
 - (1) Mix-ups, contamination and cross-contamination of HCT/Ps, supplies and reagents, and
 - (2) An HCT/P from being improperly made available for distribution.
- (b) *Temperature.* You must store HCT/Ps at an appropriate temperature.

- (c) *Expiration date.* Where appropriate, you must assign an expiration date to each HCT/P based on the following factors:
 - (1) HCT/P type;
 - (2) Processing, including the method of preservation;
 - (3) Storage conditions; and
 - (4) Packaging
- (d) *Corrective action.* You must take and document corrective action whenever proper storage conditions are not met.
- (e) *Acceptable temperature limits.* You must establish acceptable temperature limits for storage of HCT/Ps at each step of the manufacturing process to inhibit 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.

1271.265 Receipt, pre-distribution shipment and distribution of an HCT/P

- (a) *Receipt.* 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 on pre-established criteria designed to prevent communicable disease transmission.
- (b) *Predistribution shipment.* If you ship an HCT/Ps within your establishment or between establishments (e.g., procurer to processor) and the HCT/Ps is not available for distribution as described in paragraph (c) of this section, 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/Ps in quarantine.
- (c) *Availability for distribution.*
 - (1) Before making an HCT/P available for distribution, you must review manufacturing 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. A responsible person must document and date the determination that an HCT/P is available for distribution.
 - (2) You must not make available for distribution an HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under 1271.60, 1271.65 and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission.
 - (3) You must not make available for distribution any HCT/P manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission, 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.
- (d) *Packaging and shipping.* Packaging and shipping containers must be designed and constructed to protect the HCT/Ps from contamination. For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit.

- (e) *Procedures.* You must establish and maintain procedures, including release criteria, for the activities in paragraphs (a) and (d) of this section. You must document these activities. Documentation must include:
 - (1) Identification of the HCT/P and the establishment that supplied the HCT/P;
 - (2) Activities performed and the results of each activity;
 - (3) Date(s) of activity;
 - (4) Quantity of HCT/Ps subject to the activity; and
 - (5) Disposition of the HCT/P (e.g., identity of consignee).
- (f) *Return to inventory.* You must establish and maintain procedures to determine if an HCT/P that is returned to an establishment is suitable to be returned to inventory.

1271.270 Records

- (a) *General.* You must maintain records concurrently with the performance of each step required in this subpart and subpart C of this part. Any requirement in this part that an action be documented involves the creation of a record, which is subject to the requirements of this section. All records must be accurate, indelible and legible. The records must identify the person performing the work, 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 HCT/P involved.
- (b) *Records management system.* You must establish and maintain a records management system relating to core CGTP requirements. Under this system, records pertaining to a particular HCT/P must be maintained in such a way as to facilitate review of the HCT/Ps history before making it available for distribution and, if necessary, subsequent to the HCT/Ps release as part of a follow-up evaluation or investigation. Records pertinent to the manufacture of HCT/Ps (e.g., labeling and packaging procedures and equipment logs) must also be maintained and organized under the records management system. If records are maintained in more than one location, then the records management system must be designed to ensure prompt identification, location, and retrieval of all records.
- (c) *Methods of retention.* You may maintain records required under this subpart 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. Records stored in electronic systems must be backed up.
- (d) *Length of retention.* You must retain all records for 10 years after their creation, unless stated otherwise in this part. 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/Ps 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
- (e) *Contracts and agreements.* You must maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for you. This information must be available during an inspection conducted under 1271.400.

1271.290 Tracking

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- (a) *General.* If you perform any step in the manufacture of an HCT/P in which you handle the HCT/P, you must treat each such HCT/P in accordance with this section, to facilitate the investigation of actual or suspected transmission of communicable disease and take appropriate and timely corrective action.
- (b) *System of HCT/P tracking.*
 - (1) You must establish and maintain a system of HCT/P tracking that enables the tracking of all HCT/Ps from:
 - (i) The donor to the consignee or final disposition; and
 - (ii) The consignee or final disposition to the donor.
 - (2) Alternatively, if you are an establishment that performs some but not all of the steps in the manufacture of an HCT/P in which you handle the HCT/P, you may participate in a system of HCT/P tracking established and maintained by another establishment responsible for other steps in the manufacture of the same HCT/P, provided that the tracking system complies with all requirements of this section.
- (c) *Distinct identification code.* As part of your tracking system, you must ensure: That each HCT/P that you manufacture is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P; and that labeling includes information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor.
 - (1) Except as described in 1271.55 (a)(1) you must create such a code specifically for tracking, and it may not include an individual's name, social security or medical record number. You may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or may assign a new code. If you assign a new code to an HCT/P, you must establish and maintain procedures for relating the new code to the old code.
- (d) *Tracking from consignee to donor.* As part of your tracking system, you must establish and maintain a method for recording the distinct identification code and type of each HCT/P distributed to a consignee to enable tracking from the consignee to the donor.
- (e) *Tracking from donor to consignee or final disposition.* 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 for final disposition. The information you maintain must permit the prompt identification of the consignee of the HCT/P, if any.
- (f) *Consignees.* 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 this section and of the tracking system that you have established and are maintaining to comply with these requirements.
- (g) *Requirements specific to dura mater donors.* 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 transmissible spongiform encephalopathy, and to enable appropriate disposition of any affected non-administered dura mater tissue, if necessary.

1271.320 Complaint file

- (a) *Procedures.* You must establish and maintain procedures for the review, evaluation and documentation of complaints, as defined in 1271.3(aa), relating to core current good tissue practice (CGTP) requirements, and the investigation of complaints as appropriate.
- (b) *Complaint file.* 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 represent a trend. You must make the complaint file available for review and copying upon request from the FDA.
- (c) *Review and evaluation of complaints.* You must review and evaluate each complaint relating to core CGTP requirements to determine if the complaint is related to an HCT/P deviation or to an adverse reaction, and to determine if a report under 1271.350 or another applicable regulation is required. As soon as practical, you must review, evaluate and investigate each complaint that represents an event required to be reported to FDA, as described in 1271.350. You must review and evaluate a complaint relating to core CGTP requirements that does not represent an event required to be reported 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.

SUBPART E – ADDITIONAL REQUIREMENTS FOR ESTABLISHMENTS DESCRIBED IN 1271.10

1271.330 Applicability

The provisions set forth in this subpart are being implemented for non-reproductive HCT/Ps described in 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and for the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the act, or are biological products regulated under section 351 of the Public Health Service Act, are not subject to the regulations set forth in this subpart.

1271.350 Reporting

- (a) *Adverse reaction reports*
 - (1) You must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. You must report to FDA an adverse reaction involving a communicable disease if it:
 - (i) Is fatal;
 - (ii) Is life-threatening;
 - (iii) Results in permanent impairment of a body function or permanent damage to body structure; or

- (iv) Necessitates medical or surgical intervention, including hospitalization
 - (2) You must submit each report on a Form FDA-3500A to the address in paragraph (a)(5) of this section within 15 calendar days of initial receipt of the information.
 - (3) You must, as soon as practical, investigate all adverse reactions that are the subject of these 15-day reports and must submit follow-up reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a follow-up report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.
 - (4) You may obtain copies of the reporting form (FDA-3500A) from the Center for Biologics Evaluation and Research (see address in paragraph (a)(5) of this section). Electronic Form FDA-3500A may be obtained at <http://www.fda.gov/medwatch> or at <http://www.hhs.gov/forms>.
 - (5) You must submit two copies of each report described in this paragraph to the Center for Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448. FDA may waive the requirement for the second copy in appropriate circumstances.
- (b) *Reports of HCT/P deviations.*
- (1) You must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step.
 - (2) 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. 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).
 - (3) You must report each such HCT/P deviation that relates to a core CGTP requirement on Form FDA-3486 available at <http://www.fda.gov/cber/biodev/bpdrform.pdg>, within 45 days of the discovery of the event 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.

1271.370 Labeling

The following requirements apply in addition to 1271.55, 1271.60, 1271.65 and 1271.90:

- (a) You must label each HCT/P made available for distribution clearly and accurately.
- (b) The following information must appear on the HCT/P label:
 - (1) Distinct identification code affixed to the HCT/P container, and assigned in accordance with 1271.290(c);
 - (2) Description of the type of HCT/P;

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- (3) Expiration date, if any; and
 - (4) 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, instead, accompany the HCT/P.
- (c) The following information must either appear on the HCT/P label or accompany the HCT/P:
- (1) Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution;
 - (2) Storage temperature;
 - (3) Other warnings, where appropriate; and
 - (4) Instructions for use when related to the prevention of the introduction, transmission or spread of communicable diseases.

SUBPART F – INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 1271.10

1271.390 Applicability

As noted in the "Introduction," FDA has posted information on its Web site about inspections. On the Xytex Web site is a summary of preparing for FDA inspections.

The provisions set forth in this subpart are applicable only to HCT/Ps described in 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and to the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the act, or are biological products regulated under section 351 of the Public Health Service Act, are not subject to the regulations set forth in this subpart.

1271.400 Inspections

- (a) If you are an establishment that manufactures HCT/Ps described in 1271.10, whether or not under contract, you must permit the Food and Drug Administration (FDA) to inspect any manufacturing location at any reasonable time and in a reasonable manner to determine compliance with applicable provisions of this part. The inspection will be conducted as necessary in the judgement of the FDA and may include your establishment, facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers and controls required to be maintained under the part. The inspection may be made with or without prior notification and will ordinarily be made during regular business hours.
- (b) The frequency of inspection will be at the agency's discretion.
- (c) FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as necessary to determine compliance with the provisions of this part.
- (d) FDA's representative may take samples, may review and copy any records required to be kept under this part and may use other appropriate means to record evidence of observations during inspections conducted under this subpart.
- (e) The public disclosure of records containing the name or other positive identification of donors or recipients of HCT/Ps will be handled in accordance

with FDA's procedures on disclosure of information as set forth in parts 20 and 21 of this chapter.

1271.420 HCT/Ps offered for import

- (a) Except as provided in paragraphs (c) and (d) of this section, when an HCT/P is offered for import, the importer of record must notify either before or at the time of importation, the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the HCT/P is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part and must provide sufficient information for FDA to make an admissibility decision.
- (b) Except as provided in paragraphs (c) and (d) of this section, an HCT/P offered for import must be held intact by the importer or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The HCT/P may be transported under quarantine to the consignee, while the FDA district reviews the documentation accompanying the HCT/P. When FDA makes a decision regarding the admissibility of the HCT/P, FDA will notify the importer of record.
- (c) This section does not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use.
- (d) This section does not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in this part, except that paragraphs (a) and (b) of this section apply when circumstances occur under which such imparted peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission which indicates the need to review the information referenced in paragraph (a) of this section.

1271.440 Orders of retention, recall, destruction and cessation of manufacturing

- (a) Upon an agency finding that there are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in this part and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or an establishment is in violation of the regulations in this part and, therefore, does not provide adequate protection against the risks of communicable disease transmission, the Food and Drug Administration (FDA) may take one or more of the following actions:
 - (1) Serve upon the person who distributed the HCT/P a written order that the HCT/P be recalled and/or destroyed, as appropriate, and upon persons in possession of the HCT/P that the HCT/P must be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or the safety of the HCT/P is confirmed.
 - (2) Take possession of and/or destroy the violative HCT/P; or
 - (3) Serve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved. When FDA determines there are reasonable grounds to believe there is a danger

to health, such order will be effective immediately. In other situations, such order will be effective after one of the following events, whichever is later:

- (i) Passage of 5 working days from the establishment's receipt of the order; or
 - (ii) If the establishment requests a hearing in accordance with paragraph (e) of this section and part 16 of this chapter, a decision in, and in accordance with, those proceedings.
- (b) A written order issued under paragraph (a) of this section will state with particularity the facts that justify the order.
- (c) (1) A written order issued under paragraph (a)(1) of this section will ordinarily provide that the HCT/P be recalled and/or destroyed within 5 working days from the date of receipt of the order. After receipt of an order issued under paragraph (a)(1) of this section, the establishment in possession of the HCT/P must not distribute or dispose of the HCT/P in any manner except to recall and/or destroy the HCT/P consistent with the provisions of the order, under the supervision of an authorized FDA representative.
- (2) In lieu of paragraph (c)(1) of this section, other arrangements for assuring the proper disposition of the HCT/P may be agreed upon by the person receiving the written order and FDA. Such arrangements may include, among others, providing FDA with records or other written information that adequately assure that the HCT/P has been recovered, processed, stored and distributed in conformance with this part, and that, except as provided under 1271.60, 1271.65 and 1271.90, the donor of the cells or tissue for the HCT/P has been determined to be eligible.
- (d) A written order issued under paragraph (a)(3) of this section will specify the regulations with which you must achieve compliance and will ordinarily specify the particular operations covered by the order. After receipt of an order that is in effect and issued under paragraph (a)(3) of this section, you must not resume operations without prior authorization of FDA.
- (e) The recipient of an order issued under this section may request a hearing in accordance with part 16 of this chapter. To request a hearing, the recipient of the written order or prior possessor of such HCT/P must make the request within 5 working days of receipt of a written order for retention, recall, destruction and/or cessation (or within 5 working days of the agency's possession of a HCT/P under paragraph (a)(2) of this section), in accordance with part 16 of this chapter. Upon request under part 16 of this chapter, FDA will provide an opportunity for an expedited hearing for an order of cessation that is not stayed by the Commissioner of Food and Drugs.
- (f) FDA will not issue an order of destruction of reproductive tissue under paragraph (a)(1) of this section, nor will it carry out such destruction itself under paragraph (a)(2) of this section.

Dated June 17, 2004

Lester Crawford, *Acting Commissioner of Food and Drugs*

Tommy G. Thompson, *Secretary of Health and Human Services*