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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1271

[Docket No. 1997N-0484T]

Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is issuing an interim final rule to amend certain regulations regarding the screening and testing of donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps), and related labeling. FDA is taking this action in response to comments from affected interested persons regarding the impracticability of complying with certain regulations as they affect particular HCT/Ps.

DATES: The interim final rule is effective May 25, 2005. Submit written or electronic comments on the interim final rule by *[insert date 90 days after date of publication in the Federal Register]*.

ADDRESSES: You may submit comments, identified by Docket No. 1997N-0484T, by any of the following methods:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

- E-mail: fdadockets@oc.fda.gov. Include Docket No. 1997N-0484T in the subject line of your e-mail message.

- FAX: 301-827-6870.

- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:
Division of Dockets Management (HFA-305), Food and Drug Administration,
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. for this rulemaking. All comments received will be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see section IX in the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

We (FDA), have issued three final rules to implement a comprehensive new system for regulating HCT/Ps in part 1271 (21 CFR part 1271). The final rules are as follows:

- Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing (66 FR 5447, January 19, 2001) (registration final rule);
- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (69 FR 29786, May 25, 2004) (donor-eligibility final rule); and
- Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement (69 FR 68612, November 24, 2004) (CGTP final rule).

This interim final rule is making changes in response to comments from affected interested persons regarding the impracticability of complying with certain regulations as they affect particular HCT/Ps, as well as certain other editorial changes.

II. Legal Authority

We are issuing these regulations under the authority of section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264). By authority delegated under that section, we may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. Intrastate transactions affecting interstate communicable disease transmission may also be regulated under section 361 of the PHS Act. (See *Louisiana v. Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).) This interim final rule addresses the impracticability of complying with certain regulations that affect particular HCT/Ps.

III. Issuance of an Interim Final Rule; Effective Date

Under the provisions of the Administrative Procedure Act at 5 U.S.C. 553(b)(B) and FDA's administrative practices and procedures regulations at § 10.40(e)(1) (21 CFR 10.40(e)(1)), the Commissioner of Food and Drugs (the

Commissioner) finds that use of prior notice and comment procedures for issuing this interim final rule is contrary to the public interest. In addition, the Commissioner finds good cause under 5 U.S.C. 553(d)(3) and § 10.40(c)(4)(ii) for making this interim final rule effective May 25, 2005.

We conclude that this interim final rule is necessary to assure that the changes become effective concurrently with the donor-eligibility final rule and the CGTP final rule on May 25, 2005. In this way, establishments will not be required to take steps to comply with the provisions that will be replaced by the changes set out in this rule, and certain HCT/Ps will continue to be available. If the rule is not effective immediately (before the agency could take comment on a proposed rule and issue a final rule), delay could result in certain HCT/Ps being unavailable for donation. Based on existing donation practices, we believe that delay would increase the risk that some patients will not be able to obtain certain donated HCT/Ps.

Although we are publishing this regulation as an interim final rule without prior notice and comment on a proposed rule, we are providing opportunity for comment on this interim final rule. After reviewing public comment submitted to the docket, we will issue a final rule.

IV. Provisions of the Interim Final Rule

We are making the following changes to part 1271.

A. Sections 1271.55 and 1271.290

Section 1271.55 describes:

- The records that must accompany the HCT/P at all times once the donor-eligibility determination is made (§ 1271.55(a));
- The summary of records used to make the donor-eligibility determination (§ 1271.55(b));

- The deletion of personal information (§ 1271.55(c)); and
- The record retention requirements (§ 1271.55(d)).

Section 1271.55(a)(1) requires you to affix a distinct identification code to the HCT/P container, e.g., an alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P. In the interest of confidentiality, the distinct identification code must not include an individual's name, social security number, or medical record number. We make an exception to this prohibition for autologous or directed reproductive donations because in such donations, the donor is already known to the recipient.

This interim final rule adds to this exception donations made by first-degree or second-degree blood relatives. Donors who are first-degree or second-degree blood relatives know and are known by the recipient, similar to directed reproductive donations. Adding this exception may increase the comfort of the recipient by helping to confirm that the HCT/P is from the designated donor.

The revision to § 1271.290 is a technical change to reference the provisions in § 1271.55(a)(1).

B. Section 1271.80

Section 1271.80 describes the general requirements for donor testing, such as:

- The requirement to test for relevant communicable diseases;
- Timing of specimen collection;
- What tests to use; and
- Who is an ineligible donor.

The interim final rule revises the requirements regarding timing of the specimen collection. We deleted the statement in § 1271.80(b) regarding

specimen collection at the time of recovery, because we are aware that this has been interpreted to mean that a testing specimen collected from a donor on the day of donation is superior. We believe that, for a cadaveric donor, either a pre-mortem specimen collected within 7 days before death or a post mortem specimen are appropriate specimens. However, the pre-mortem specimen, if available, may be preferable because it is likely to be less hemolyzed, and excessive hemolysis can interfere with the test results. In addition, a cadaveric donor may have received fluid infusions prior to death, resulting in plasma dilution sufficient to affect test results. For these reasons, a specimen collected on the day of donation from a cadaveric donor may not be superior to a specimen collected within 7 days before death.

The interim final rule also modifies the timing of sample collection for donors of bone marrow (when considered an HCT/P under § 1271.3(d) (21 CFR 1271.3(d))) and oocytes. The change will permit the collection of a donor specimen for testing up to 30 days before recovery of the HCT/P for these additional HCT/Ps. In the donor-eligibility final rule we state that we permit collection of the donor specimen up to 30 days before recovery for donors of peripheral blood stem/progenitor cells due to the myeloablative treatment regimen and the need to determine the eligibility of the donor before the recipient's treatment begins (69 FR 29786 at 29808). Because this reasoning also applies to donors of bone marrow covered by the HCT/P regulations and donors of oocytes who must undergo conditioning regimens beginning more than 7 days before recovery of oocytes, we have included a reference to bone marrow and oocytes in § 1271.80(b) to permit testing up to 30 days before recovery.

C. Section 1271.90

Section 1271.90(a) describes exceptions to the requirement for donor-eligibility determination and related labeling requirements. The exceptions apply to the following HCT/Ps:

- Cells and tissues for autologous use;
- Reproductive cells or tissue donated by a sexually intimate partner of the recipient; and
- Cryopreserved cells or tissue for reproductive use, other than embryos, intended for directed donation.

In the donor eligibility final rule at § 1271.90(a)(2), a donor eligibility determination is not required for reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use. We are now adding a new exemption from screening and testing in § 1271.90(a)(4) for cryopreserved embryos that, while originally exempt from the donor eligibility requirement because the donors were sexually intimate partners, are later 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 a recipient.

This change reflects the fact that sexually intimate partners may decide to donate their cryopreserved embryos long after their fertility treatments are completed. Because the embryos were intended for use in a sexually intimate relationship, the donors would not have been required to be screened and tested for communicable disease agents at the time that oocytes and semen were recovered. The new provision recommends that appropriate measures be taken to screen and test the semen and oocyte donors before transfer of the embryo to the recipient, when possible.

If appropriate screening and testing of the semen and oocyte donors are performed subsequent to cryopreservation and before transfer of the embryo to the recipient, the labeling requirement in § 1271.90(b)(6) applies, i.e., “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.” If screening and testing of the semen and oocyte donors are not performed, this rule would not prohibit the transfer of the embryo into a recipient. In such an event, the labeling requirements in § 1271.90(b)(2) and (b)(3) are applicable. The HCT/P must be labeled with “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” and “WARNING: Advise recipient of communicable disease risks.” This labeling would provide information to the treating physician to permit discussion with the recipient of the potential risks.

Since we issued the donor eligibility rule, we have received letters and comments in meetings concerning the importance of cryopreserved embryos to individuals seeking access to donated embryos. Donated embryos may provide a very important treatment to some individuals. For example, a couple may not be able to conceive a child because the female partner has had her ovaries removed and the male partner has undergone chemotherapy and no longer has viable spermatozoa. In order to assure that such a treatment continues to be available, we have re-evaluated the screening and testing requirements imposed by these rules. Screening and testing of semen and oocyte donors is recommended given the potential risk that such tissue, like any cell or tissue derived from the human body, could transmit communicable disease. However, it is possible that the couple would not be available for screening and testing due to refusal of a partner or death. In such instances,

the embryo would be labeled as required under the rule, and this rule would not prohibit the transfer of the embryo.

We believe this change will enhance the availability of embryos for donation. However, we are soliciting comments on the effectiveness of this change to enhance the availability of embryos, and the potential benefits, risks, and any other direct or indirect effects of this change. Section 1271.90(b) contains labeling requirements for the previously described HCT/Ps excepted from the donor-eligibility determination requirements. We are revising § 1271.90(b) to clarify when each required label is appropriate for the HCT/Ps described in § 1271.90(a), i.e., autologous cells and tissues, reproductive cells and tissues donated by a sexually intimate partner, and cryopreserved reproductive cells and tissues, including embryos, where the donor(s) was not screened and tested at the time of collection. We have also clarified § 1271.90(b)(3), that cells and tissues for autologous use do not require the label “Advise patient of communicable disease risk” because the patient’s own cells or tissues are being returned, and in this situation, there is minimal, if any, risk.

D. Section 1271.370

Section 1271.370 contains labeling requirements in addition to §§ 1271.55, 1271.60, 1271.65, and 1271.90 for HCT/Ps regulated solely under section 361 of the PHS Act and part 1271, e.g., distinct identification code, expiration date, and warnings. We are revising § 1271.370(b)(4) to state that if applying the applicable warnings to the container is physically impossible, then the labeling must, instead, accompany the HCT/P. This change is necessary because the container for some HCT/Ps, such as those used for semen cryopreservation, is so small that it does not accommodate the warning language. In addition,

the use of a tie-tag with warning language is not feasible because it is difficult to securely attach the tie-tag to a container stored in liquid nitrogen. In such cases, the warning language must accompany the HCT/P.

V. Analysis of Impacts

FDA has examined the impacts of the interim final rule under Executive Order 12866 as well as under the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this interim final rule is not an economically significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule makes certain issued regulations affecting reproductive and hematopoietic stem cell HCT/Ps more practicable, and does not impose any new requirements, FDA certifies that the interim final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after

adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this interim final rule to result in any 1-year expenditure that would meet or exceed this amount.

VI. The Paperwork Reduction Act of 1995

This interim final rule contains no collections of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(i) and (j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this interim final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the interim final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the interim final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this interim final rule. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are

to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR 1271

Biological Drugs, Communicable diseases, HIV/AIDS, Human cells, tissues, and cellular and tissue-based products, Medical Devices Reporting and recordkeeping requirements.

■ Therefore, under the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, Chapter I of title 21 of the Code of Federal Regulations is amended as follows:

PART 1271—HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

■ 1. The authority citation for 21 CFR part 1271 continues to read as follows:

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

■ 2. Section 1271.55 is amended by revising paragraph (a)(1) to read as follows:

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

(a) * * *

(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;

* * * * *

■ 3. Section 1271.80 is amended by revising paragraph (b) to read as follows:

§ 1271.80 What are the general requirements for donor testing?

* * * * *

(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.

* * * * *

■ 4. Section 1271.90 is amended by revising paragraphs (a)(3) introductory text and (b), and by adding paragraph (a)(4) to read as follows:

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

(a) * * *

(3) Cryopreserved cells or tissue for reproductive use, other than embryos, originally exempt under paragraphs (a)(1) or (a)(2) of this section at the time of donation, that are subsequently intended for directed donation, provided that

* * * * *

(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.

■ 5. Section 1271.290 is amended by revising the second sentence in paragraph (c) to read as follows:

§ 1271.290 Tracking.

* * * * *

(c) * * * 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 number, or medical record number. * * *

* * * * *

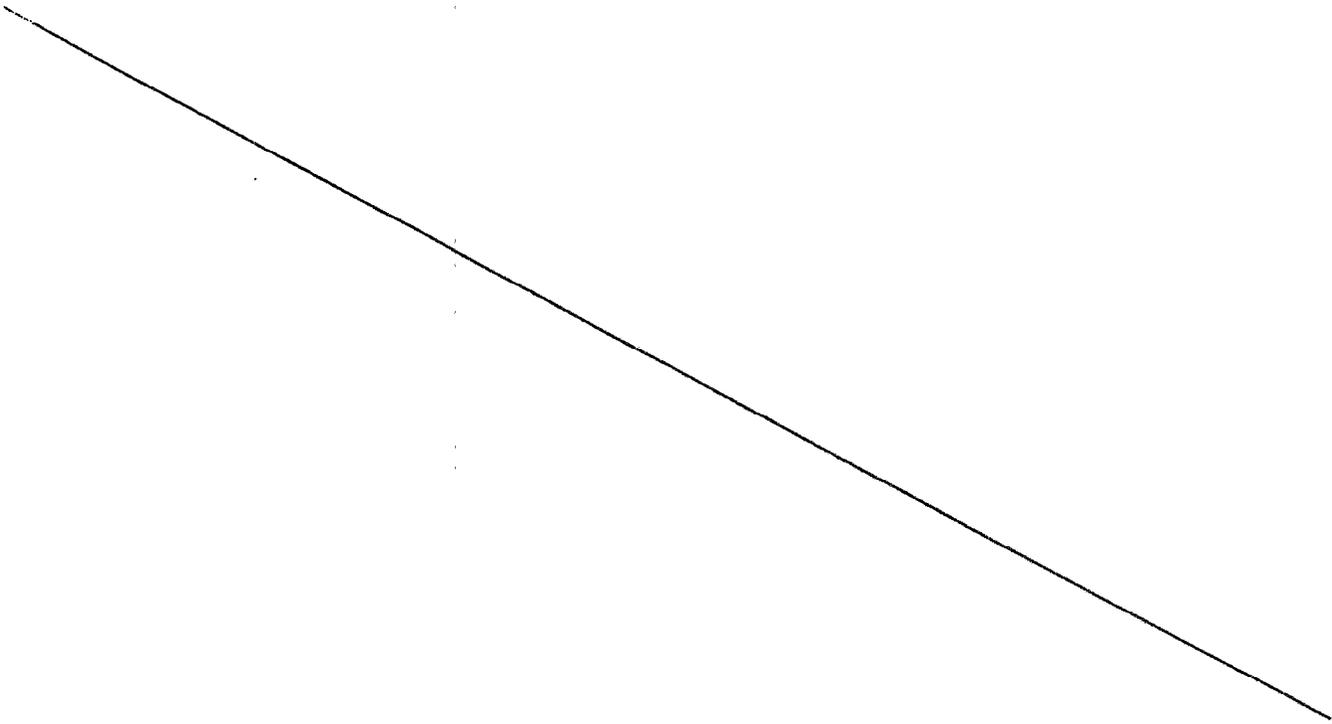
■ 6. Section 1271.370 is amended by revising paragraph (b)(4) to read as follows:

§ 1271.370 Labeling.

* * * * *

(b) * * *

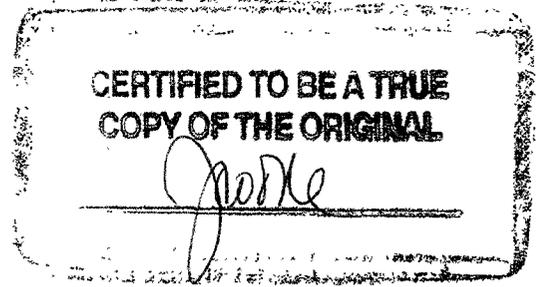
(4) Warnings required under § 1271.60(d)(2), § 1271.65(b)(2), or § 1271.90(b), if applicable and physically possible. If it is not physically



possible to include these warnings on the label, the warnings must, instead, accompany the HCT/P.

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Dated: 5/23/05
May 23, 2005.



J. Shuren
Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 05-????? Filed ??-??-05; 8:45 am]

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