

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

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**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:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is adopting as a final rule, without change, the provisions of the interim final rule that amended 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 to complete the rulemaking initiated with the interim final rule.

**DATES:** This rule is effective [*insert date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Brenda R. Friend, 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**

In the **Federal Register** of May 25, 2005 (70 FR 29949), FDA issued an interim final rule on Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling (hereinafter referred to as the interim final rule). These regulations became effective upon

the date of publication in the **Federal Register**. We issued the interim rule to assure that the changes became effective concurrently with the Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products final rule (69 FR 29786, May 25, 2004) and the Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement final rule (69 FR 68612, November 24, 2004) on May 25, 2005. In this way, establishments were not required to take steps to comply with the provisions in part 1271 (21 CFR part 1271) that were replaced by the changes set out in the interim final rule, and certain HCT/Ps would continue to be available.

## **II. Comments on the Interim Final Rule and FDA Responses**

We received several comments on the interim final rule. To make it easier to identify comments and our responses, the word “Comment,” in parentheses, will appear before the comment’s description, and the word “Response,” in parentheses, will appear before our response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value or importance or the order in which it was received.

(Comment 1) A comment appreciated and applauded the change to § 1271.370(b)(4) to allow labeling with warning(s) to accompany the HCT/P when the HCT/P container is too small to accommodate the warning(s) on the label. Another comment expressed concern that the accompanying labeling could be ignored or lost.

(Response) We acknowledge and appreciate the supportive comment. This requirement addresses the situation where it is not physically possible to

include warnings directly on the HCT/P label, either because the container is too small or the HCT/P is cryopreserved, which may interfere with adherence of label materials. In these situations, the warnings must accompany the HCT/P.

We acknowledge the comment's concern that it is better to provide information on the HCT/P's label. However, we permit other important information, such as the summary of records, to accompany the HCT/P; such important information is not present on the HCT/P label. We believe that consignees are generally careful to make sure information accompanying HCT/Ps is not ignored or lost, and we believe that the accompanying information will be available. Necessity compels this authorization for certain information to accompany an HCT/P when it is not possible to include it on the label, and we conclude that it is adequate to provide such information in accompanying documents when it is necessary to do so.

(Comment 2) A comment noted that § 1271.55(a)(1) requirements (i.e., affixing a distinct identification code to the HCT/P container) were clearly designed to maintain donor anonymity. However, the comment asked if fertility clinics could write in information about the recipient (e.g., name, account number) because by the time a donor's HCT/P is collected, a specific recipient has already been identified. The comment stated that fertility clinics, for example, never collect anonymously donated oocytes without already having a recipient identified and ready to receive the donation.

(Response) The requirements in § 1271.55(a)(1) are focused on protecting the identity of the donor in the interest of confidentiality. We note that this provision prescribes how an establishment must label the HCT/P before releasing it for distribution, but does not prohibit the addition of the recipient's

name once the donor eligibility determination is completed and the reproductive HCT/P is released for distribution. For an oocyte donation, the release determination is likely to be completed very soon after collection.

(Comment 3) A few comments suggested changes to the timing of the specimen collection in § 1271.80(b). In particular, a comment noted that § 1271.80(b)(1) permits testing on oocyte donors up to 30 days before recovery, while § 1271.80 seems to maintain a 7-day testing window for semen donors, whose spermatozoa will combine with the oocytes to create an embryo for a gestational carrier cycle, and stated that both these donors should have a 30-day testing window.

Another comment stated that testing donors of sperm, oocytes, and embryos at the time of donation is “superior” but noted that the American Association of Tissue Banks guidelines for accredited tissue banks recommend that all donors be tested within 7 days of collection. The comment recommended that FDA go back to 7-day testing. One comment recommended that any individual intending to cryopreserve his/her HCT/P be tested 7 to 10 days prior to cryopreservation or within a short period after cryopreservation.

(Response) The interim final rule modified the timing of blood specimen collection for oocyte donors to permit the determination of donor eligibility before the donor’s conditioning regimen begins. We did not change the timing of blood specimen collection for semen donors, because they do not undergo any conditioning regimen.

Collecting blood specimens from donors of semen, oocytes, and embryos at the time of donation is sometimes impractical because of the time it takes to obtain the test results. We have made exceptions to the requirement for testing within 7 days in situations where the donor has to undergo

conditioning in advance. This is also the case where the recipient undergoes myeloablative treatment and there is a need to determine the eligibility of the donor before the recipient's treatment. Establishments are welcome to establish more restrictive testing criteria as noted in the American Association of Tissue Banks standards.

(Comment 4) A comment responded to FDA's solicitation for comments on the effectiveness of § 1271.90(a)(4), (a new exception from the donor-eligibility determination requirement for certain cryopreserved embryos) to enhance the availability of embryos, and the potential benefits, risks, and any other direct or indirect effects of this change. The comment pointed out that cryopreserved embryos (and HCT/Ps) are often exposed to liquid nitrogen, and research articles have reported that hepatitis B and bovine hepatitis virus can be transmitted through liquid nitrogen contamination. Therefore, cryopreserved embryos from untested semen and oocyte donors, commingling with cryopreserved embryos from tested donors, may place recipients, cryostorage centers, and assisted reproductive technology facilities at risk. Simply having warning(s) appear on the label of the cryopreserved HCT/P specimen from an untested donor, under revised §§ 1271.90(b)(2) and (b)(3), or having the warning(s) accompany such HCT/Ps, under revised § 1271.370(b)(4), would not eliminate the risks and may even result in an increased number of tort cases.

(Response) We decline to require separate storage for tested and untested HCT/Ps, though establishments may choose to utilize physically separated areas for tested and untested HCT/Ps. To reduce risk of contamination/cross-contamination from HCT/Ps that are untested or determined ineligible because of a reactive screening test, reproductive establishments could verify or

validate that the cryocontainers (vials or straws) meet specifications and are not subject to breakage at the temperatures and conditions at which they are stored. Verification could be accomplished by the establishment that uses the cryocontainers or by the vendor that supplies the cryocontainers.

(Comment 5) A comment recommended a quarantine period of 6 months for any reproductive HCT/P from directed donors and anonymous donors, including anonymous donors whose identity might be disclosed. The comment also recommended mandatory retesting of oocyte donors (for donated embryos created using a donor oocyte) and embryo donors (semen and oocyte donors) prior to transfer of the donated HCT/P.

(Response) In the Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products final rule (69 FR 29786 at 29800), we explained why quarantine and retesting are required for anonymous semen donors but not for other reproductive donors. We considered comments concerning decreased pregnancy success rates for cryopreserved semen from directed donors and for cryopreserved embryos. In addition, techniques for the successful cryopreservation of oocytes are still being developed. Accordingly, we have declined to increase quarantine requirements for oocyte and embryo donations.

(Comment 6) A comment requested clarification on the use of the warning “FOR AUTOLOGOUS USE ONLY” under § 1271.90(b)(1), and particularly, FDA’s definition of “autologous” for certain circumstances related to in vitro fertilization.

(Response) We define “autologous” in § 1271.3(a) as meaning the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.

Transfer of an embryo into the woman who contributed the oocytes would not be considered autologous because the embryo is formed by gametes from two individuals. This means that in the circumstances related to in vitro fertilization, use of a label “FOR AUTOLOGOUS USE ONLY” would not be appropriate for labeling a cryopreserved embryo. Other labeling requirements listed in § 1271.90(b) would apply based on the test status of the gamete donors.

(Comment 7) We received several comments that, although they relate to significant issues, are not relevant to the interim final rule. These comments concerned: (1) A request that donors with a curable communicable disease be eligible to donate reproductive HCT/Ps after receiving treatment and retesting negative for the communicable disease; (2) the definition of “responsible person” under § 1271.3(t); (3) certification or registration requirements, other than those applicable under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a), for a clinical laboratory to perform donor screening; and (4) issues associated with the storage of embryos and other HCT/Ps, but unrelated to the potential for transmission of communicable disease (e.g., abandonment, legal responsibility, and nonpayment).

(Response) These comments are on matters outside the scope of the interim final rule and this final rule. Relevant communicable disease agent or disease was addressed in previously finalized portions of part 1271, subpart C. The definitions in § 1271.3 were not discussed or addressed in the interim final rule. Registration requirements applicable to testing laboratories are addressed in part 1271, subparts A and B, and certification requirements are discussed in part 1271, subpart C. FDA expects that the contractual agreement between the cryostorage facility and the individual(s) storing the HCT/P will

address financial and legal issues unrelated to the potential for communicable disease transmission.

### **III. Analysis of Impacts**

FDA has examined the impacts of the final rule under Executive Order 12866 and 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 analysis of costs and benefits of available regulatory alternatives contained in the interim final rule (70 FR 29949 at 29951) is adopted without change in this final rule. By now reaffirming that interim final rule, FDA has not imposed any new requirements. Therefore, there are no additional costs and benefits associated with this final rule.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule does not make any changes to the interim final rule or our analysis included therein, the agency certifies that the 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 \$122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

#### **IV. The Paperwork Reduction Act of 1995**

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

#### **V. 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.

#### **VI. Federalism**

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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 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.

#### **List of Subjects in 21 CFR Part 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, 21 CFR part 1271 is amended as follows:

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

■ Accordingly, the interim final rule amending 21 CFR part 1271 which was published at 70 FR 29949 on May 25, 2005, is adopted as a final rule without change.

Dated: 5/26/07

May 26, 2007.

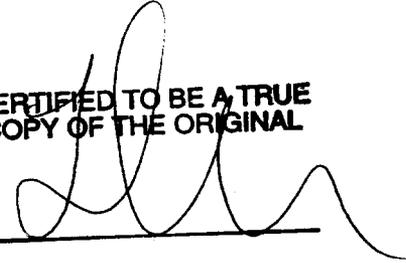
  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.

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