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21 CFR Parts 210, 211, 820, and 1271
Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule and Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210, 211, 820, and 1271

[Docket No. 1997N–0484S]

[RIN 0910–AB27]

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is requiring human cell, tissue, and cellular and tissue-based product (HCT/P) establishments to screen and test cell and tissue donors for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases. The agency is amending the current good manufacturing practice (CGMP) and quality system (QS) regulations that apply to HCT/Ps regulated as drugs, medical devices, and/or biological products to clarify the role of the new donor-eligibility regulations in relation to existing CGMP regulations. By preventing the transmission of communicable disease by the wide spectrum of HCT/Ps that are marketed now or may be marketed in the future, the agency's action will improve protection of the public health and increase public confidence in new technologies.

DATES: This rule is effective May 25, 2005. This rule is applicable to cells and tissues recovered on or after May 25, 2005.

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SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction
A. Background
B. Legal Authority
II. Highlights of the Final Rule
A. Plain Language
B. New Terminology and Definitions
C. Other Highlights
III. Comments on the Proposed Rule and FDA's Responses
A. General
B. Amendments to 21 CFR Parts 210, 211, and 820
C. Definitions (§ 1271.3)
D. Part 1271, Subpart C—Donor-Eligibility
E. Economic Impacts
IV. Analysis of Economic Impacts
A. Objectives and Basis of the Proposed Action
B. The Type and Number of Entities Affected
C. Nature of Impacts
D. Benefits of the Final Rule
E. Small Entity Impacts and Analysis of Alternatives
V. Environmental Impact
VI. Federalism Assessment
VII. The Paperwork Reduction Act of 1995
VIII. References

I. Introduction

This final rule is part of a comprehensive new system of regulation for HCT/Ps. The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products. Consolidating the regulation of HCT/Ps into one regulatory program is expected to lead to increased consistency and greater efficiency. Together, these planned improvements will increase the safety of HCT/Ps, and public confidence in their safety. We intend to make the good tissue practice final rule, which has not yet published but which FDA intends to issue soon, effective 1 year after publication of this rule. Once both this rule and the good tissue practice regulations are in effect, FDA's comprehensive regulatory framework will be complete.

A. Background

In 1997, FDA proposed a new approach to the regulation of HCT/Ps (62 FR 9721, March 4, 1997). (The term "HCT/P" is defined at § 1271.3(d) (21 CFR 1271.3(d).) To improve the regulation of HCT/Ps, we announced our intention to establish a comprehensive regulatory program for HCT/Ps, contained in part 1271 (21 CFR part 1271). In accordance with the tiered, risk-based approach that we proposed, some HCT/Ps would be regulated only under these new regulations, while others would also be regulated as drugs, devices, and/or biological products.

To implement the proposed approach, we issued three proposed rules:

- Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products (the registration proposed rule) (63 FR 26744, May 14, 1998);
- Suitability Determination for Donors of Human Cellular and Tissue-Based Products (the donor-suitability proposed rule) (64 FR 52696, September 30, 1999); and
- Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (the CGTP proposed rule) (66 FR 1508, January 8, 2001).

We published a final rule entitled "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing," in the **Federal Register** on January 19, 2001 (the registration final rule) (66 FR 5447). The registration final rule put into place general provisions pertaining to the scope and applicability of part 1271. These provisions are contained in subpart A of part 1271, along with a section that contains definitions applicable to all of part 1271 (§ 1271.3). The registration final rule requires cell and tissue establishments to register with us and submit a list of their HCT/Ps; the procedures for registration and listing are contained in subpart B of part 1271.

Some sections of the registration final rule became effective on April 4, 2001. Under those provisions, we now receive registration and listing information from establishments that engage in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation (as described in § 1271.3(d)(1)). The effective date for the remaining sections was January 21, 2003, by which time we expected to have completed rulemaking for all of part 1271 (66 FR 5447 at 5448). At that time, the registration and listing requirements would have become effective for all other HCT/Ps (as described in § 1271.3(d)(2)). However, we recognized that unanticipated delays in completing the rulemaking for the remainder of part 1271 could occur, and we noted that, should the rulemaking proceedings be delayed past the 2-year timeframe, we would consider whether to maintain the 2-year effective date for the HCT/Ps described in § 1271.3(d)(2) or whether to extend that date for some or all of these HCT/Ps (66 FR 5447 at 5449). Since the rulemaking proceedings were delayed past the original 2-year effective date of January 21, 2003, we delayed the effective date of § 1271.3(d)(2) until January 21, 2004 (68 FR 2690, January 21, 2003). After the definition became final on January 21, 2004, we issued an interim final rule excepting human dura mater and human heart valve allografts from the scope of the definition of "human cells, tissues, or cellular or tissue-based products (HCT/Ps)" (69 FR 3823, January 27, 2004). We took this action to assure that these products, which were subject to the Federal Food, Drug, and Cosmetic Act (the act) and therefore regulated under the current good

manufacturing practice regulations set out in the quality system regulations in part 820 (21 CFR part 820), were not released from the scope of those regulations before a more comprehensive regulatory framework applicable to HCT/Ps, including donor eligibility requirements, good tissue practice regulations, and appropriate enforcement provisions, is fully in place. When that comprehensive framework is in place, we intend that human dura mater and human heart valve allografts will be subject to it. We intend to revoke the interim final rule at that time.

We are now making final the donor-suitability proposed rule that was proposed on September 30, 1999. (For reasons discussed in comment 26 of this document, we refer in this final rule to donor "eligibility" rather than "suitability.") The comment period for that proposed rule closed on December 29, 1999. On April 18, 2000, we reopened the comment period for an additional 90 days. We took this step in response to requests for an extension of the comment period as well as to provide sufficient time for State officials to participate in the rulemaking (65 FR 20774, April 18, 2000).

Because of their nature as derivatives of the human body, HCT/Ps pose a risk of transmitting communicable diseases. For this reason, this final rule requires that most cell and tissue donors be tested and screened for evidence of relevant communicable disease infection. It also contains other related requirements (e.g., on records, quarantine, storage, and labeling). These donor-eligibility requirements, which locate in subpart C of part 1271, are part of the core requirements applicable both to HCT/Ps regulated solely under these regulations and section 361 (the 361 HCT/Ps) of the Public Health Service Act (the PHS Act) and to those HCT/Ps also subject to regulation as drugs, devices, and/or biological products. As part of this rulemaking, we are also amending the drug CGMP regulations and the device QS regulations to clarify the role of the donor-eligibility requirements in the manufacture of HCT/Ps subject to regulation as drugs, devices, and/or biological products.

Since the publication of the donor-suitability proposed rule, we have continued to obtain current and accurate information on the risks of communicable-disease transmission by HCT/Ps and the most appropriate testing and screening measures. To this end, we have met with FDA's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) (January 18 to 19, 2001, and June 26 to 27, 2002); the Blood Products Advisory Committee (BPAC) (December 13 to 14, 2001, and March 14 to 15, 2002); and the Centers for Disease Control and Prevention (CDC) (June 26 to 27, 2000). We have placed information on these meetings in the docket for this rulemaking.

We have used the information obtained at those meetings to develop a draft guidance document on determining donor eligibility entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (the donor-eligibility draft guidance). Elsewhere in this issue of the **Federal Register**, we announce the availability of that draft guidance, and solicit comments on its contents. We have also developed draft guidance on screening for Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) entitled "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (the CJD draft guidance) (67 FR 42789, June 25, 2002). We intend to combine the donor-eligibility draft guidance with the CJD draft guidance, and to issue a single final guidance document.

B. Legal Authority

We are issuing these new regulations under the authority of section 361 of the PHS Act (42 U.S.C. 264). Under that section, by delegation from the Surgeon General and the Secretary of Health and Human Services, FDA 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 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).)

It is especially important to recognize that HCT/P manufacturing inevitably has interstate effects. HCT/Ps recovered in one State may be sent to another for processing, then shipped for use throughout the United States, or beyond. FDA has been involved in many recalls where HCT/Ps processed in a single establishment have been distributed in many States.

Section 361 of the PHS Act authorizes FDA to issue regulations necessary to prevent the introduction, transmission, or spread of communicable diseases. Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents.

Certain diseases are transmissible through the implantation, transplantation, infusion, or transfer of HCT/Ps derived from donors infected with those diseases. To prevent the introduction, transmission, or spread of such diseases, we consider it necessary to take appropriate measures to prevent the use of cells or tissues from infected donors. Thus, these regulations require that, before the use of most HCT/Ps, the cell or tissue donor must be determined to be eligible to donate, based on the results of screening and testing for relevant communicable diseases. In most cases, a donor who tests reactive for a particular disease, or who possesses clinical evidence of or risk factors for such a disease, would be considered ineligible, and cells and tissues from that donor would not ordinarily be used.

In addition to regulations governing the testing and screening of donors for relevant communicable disease and quarantine and storage of HCT/Ps, FDA has also determined that regulations requiring establishments to maintain certain records related to HCT/Ps and to establish standard operating procedures are necessary to prevent the introduction, transmission, or spread interstate of communicable disease. A single donor may be the source of a large number of HCT/Ps. For example, it may be discovered, long after the donation and transplantations have been completed, that a donor of HCT/Ps transplanted into a large number of recipients had a relevant communicable disease. Although it might be too late to prevent the recipients' infections, it would not be too late to for the recipient to obtain treatment and take steps to avoid infecting others, such as close family members. However, unless adequate records were maintained, and maintained for the period of time throughout which infections may be identified, it would be impossible to identify the recipients potentially infected by the donor's HCTPs. This would be a critical breakdown in the prevention of disease transmission. Accordingly, FDA determined that the maintenance and retention of records are necessary to prevent the interstate introduction, transmission, and spread of communicable disease. Since some diseases, such as transmissible spongiform encephalopathies (TSEs), appear to have a long latency period, FDA has determined that a 10-year record retention period is necessary.

Similarly, it is necessary for establishments to establish, maintain,

and follow procedures related to the prevention of communicable disease. The agency has determined that these provisions are necessary to ensure that the important protections created by these regulations are actually effected and are not simply empty promises. Only manufacturing conducted in accordance with established procedures can assure that HCT/Ps meet the standards in these rules. If standardized processes are not developed and used, mistakes, inevitably, are made. Moreover, review of procedures can be critical to determining the cause of a disease transmission. Without that analysis, it would be impossible to prevent a future occurrence, with possibly fatal consequences.

These regulations are intended to prevent the transmission of communicable disease through the implantation, transplantation, infusion, or transfer of HCT/Ps. However, as noted in the registration and donor-suitability proposed rules, all HCT/Ps pose some risk of carrying pathogens that could cause disease in health-care personnel, other handlers of tissue, recipients, and family members or other contacts of recipients (63 FR 26744 and 64 FR 52696 at 52698). This broader concern for the spread of communicable disease is reflected in certain labeling requirements in these regulations and in the criteria for identifying a relevant communicable disease. We recognize that regulations exist that are specifically designed to protect employees who may come in contact with infectious materials (see 29 CFR 1910.1030, 42 CFR 72.6, and 49 CFR 173.196), and we do not consider these regulations to be in conflict with those other regulations currently in effect. However, we have made an effort to be consistent with the terminology used in these other regulations; e.g., "Infectious Substances" and the Biohazard legend.

Under section 361 of the PHS Act, FDA is authorized to enforce the regulations it issues to prevent the introduction, transmission, or spread of communicable diseases interstate through such means as inspection, disinfection, sanitation, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection in human beings, and other measures that may be necessary. In addition, under section 368(a) of the PHS Act, any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted. For organizational defendants, fines range up to $200,000 and $500,000. Individuals and organizations also face possible alternative fines based on the amount of gain or loss (18 U.S.C. 3559 and 3571(b) through (d)). Federal District Courts also have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act. (See *Califano* v. *Yamasaki*, 442 U.S. 682, 704–05 (1979); *United States* v. *Beatrice Foods Co.*, 493 F.2d 1259, 1271–72 (8th Cir. 1974), *cert. denied*, 420 U.S. 961 (1975).) Under sections 501(a)(2)(B) and (h), and 520(f)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351(a)(2)(B) and (h), and 21 U.S.C. 360j(f)(1)), drugs (including biological products) and devices (including biological products) are subject to CGMP requirements designed to ensure, among other things, product safety (21 U.S.C. 351(a)(2)(B) and (h), and 21 U.S.C. 360j(f)(1)). The authorities supporting the CGMP and QS regulations are also applicable when the CGMP and QS regulations apply to an HCT/P regulated as a drug, biological product, or device. Currently, the CGMP and QS regulations applicable to HCT/Ps regulated as drugs or devices do not delineate testing and screening procedures for communicable diseases. (See parts 210, 211, and 820 (21 CFR parts 210, 211, and 820).) Nevertheless, we consider communicable-disease testing and screening to be steps in the manufacturing process that are crucial to the safety of such products. As a result, we are amending the existing CGMP regulations for drugs in parts 210 and 211 and the QS regulations for devices in part 820, which include CGMP requirements, to make clear that the testing and screening provisions of part 1271 subpart C apply to HCT/Ps regulated as drugs, devices, and/or biological products.

Under § 210.1(c), the manufacturer of an HCT/P regulated as a drug, including a biological product that is a drug under the act, must comply with the donor-eligibility procedures in part 1271, subpart C. Failure to follow the CGMP requirements, including the testing and screening procedures in part 1271, would make the product adulterated under the act. In issuing this regulation, FDA is relying on the drug CGMP authorities (in particular, section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)), as well as section 361 of the PHS Act. Under § 820.1(a)(1), the manufacturer of an HCT/P regulated as a device, including a biological product that is a device under the act, must comply with the same procedures.

Section 375 of the PHS Act provides for Federal oversight of the nation's Organ Procurement and Transplantation Network, and section 379 of the PHS Act authorizes the National Bone Marrow Donor Registry (42 U.S.C. 274c and 274k). The Health Resources and Services Administration (HRSA) currently administers both of these programs. Given HRSA oversight in these areas, vascularized human organs (to include vascularized subparts of human organs) and minimally manipulated bone marrow (as defined in § 1271.3(d)(2)) for unrelated allogeneic use are specifically excluded from these final regulations.

II. Highlights of the Final Rule

This final rule requires establishments to make donor-eligibility determinations for cell and tissue donors, based on donor screening and testing for relevant communicable disease agents and diseases (§ 1271.45). The regulations cover how to screen and test donors (§§ 1271.75, 1271.80, and 1271.85), as well as how to make the donor-eligibility determination (§ 1271.50). The term "relevant communicable disease agent or disease" is defined at § 1271.3(r). The rule also contains related requirements pertaining to procedures (§ 1271.47); records (§ 1271.55); quarantine (§ 1271.60); and storage of HCT/Ps from ineligible donors (§ 1271.65). Two of these provisions describe situations where it is not prohibited to use an HCT/P from an ineligible donor or a donor who has not yet been determined eligible (§§ 1271.60 and 1271.65). Exceptions from the requirement for making a donor-eligibility determination appear in § 1271.90.

The donor-eligibility draft guidance that may be found elsewhere in this **Federal Register** is intended to assist establishments in complying with the requirements of this final rule and contains details that are not in the regulation. Although not binding, the draft guidance presents the agency's current thinking on the topics covered. For example, whereas the regulation requires an establishment to screen donors for risk factors, the draft guidance specifies what we consider those risk factors to be. Similarly, the draft guidance contains recommendations on which tests to use to comply with the testing requirements in §§ 1271.80 and 1271.85. The draft guidance also identifies several additional disease agents or diseases that we believe meet the definition of relevant communicable disease agent or

disease. We welcome comments on the draft guidance. As scientific knowledge is developed, new tests are introduced, and additional relevant communicable disease agents and diseases are identified, we intend to follow the good guidance practices set out in § 10.115 to modify the donor-eligibility guidance so that it remains current.

A. Plain Language

In the **Federal Register** of June 10, 1998 (63 FR 31885), the Presidential Memorandum on Plain Language in Government Writing was issued. The goal of the plain language initiative is to publish government documents that are easier to understand.

In response to this initiative, we have written the donor-eligibility regulation in plain language. We have taken the following actions:

- Written the regulation in question-and-answer format;
- Reorganized some regulatory sections for greater clarity; and
- Followed other plain-language conventions, such as using "must" instead of "shall."

The resulting codified language is easier to read and understand than the proposed regulation. These editorial changes are for clarity only and do not change the substance of the requirements.

B. New Terminology and Definitions

In the registration final rule, we discussed our decision to replace the term "human cellular or tissue-based products" with "human cells, tissues, and cellular and tissue-based products" (abbreviated HCT/Ps) (66 FR 5447 at 5455). For consistency, we have made the same change in this final rule.

In response to comments, we have changed the term "donor suitability" to "donor eligibility."

In addition, we have made several changes to the definition of "relevant communicable disease agent or disease" with respect to prevalence. We intend the new language to cover both intentional and unintentional release of infectious agents.

We have also modified the definition of "directed donor" and changed the term to "directed reproductive donor."

We have deleted the definitions of "xenotransplantation" and "close contacts."

C. Other Highlights

This final rule contains other changes from the proposed rule. These changes are listed as follows:

- Provisions in § 1271.47, originally proposed in the CGTP proposed rule, require that HCT/P establishments establish and maintain procedures for the steps they perform in determining donor eligibility, including testing and screening;
- The requirement for donor retesting 6 months after donation now applies only to anonymous semen donors. In addition, you do not have to obtain a specimen for testing at each donation from a repeat anonymous donor, so long as you do not release the donation unless the donor has been retested (at least 6 months post donation). Directed donations of semen are excepted from the retesting requirement;
- Physical separation between HCT/Ps from ineligible and eligible donors is no longer required;
- We have removed the requirement that a physician must consent to the use of an HCT/P from an ineligible donor;
- You must screen all donors for *Treponema pallidum* and some donors for Human T-lymphotropic virus (HTLV) (in addition to testing);
- You must screen donors for "communicable disease risks associated with xenotransplantation." Under the proposed rule, receipt of a xenotransplantation product would have made a donor ineligible under all circumstances. Now, receipt of a xenotransplantation product no longer overrides the special circumstances, listed in § 1271.65(b)(1), under which use of an HCT/P from an ineligible donor is not prohibited;
- We have modified the requirements applicable to testing for Cytomegalovirus (CMV);
- If the donor is one month of age or younger, you must test a specimen from the birth mother;
- The requirements on timing of specimen collection allow 7 days before or after recovery, or for donors of peripheral blood stem progenitor cells only, up to 30 days before recovery, if specimen collection at the time of recovery is not feasible; and
- Required testing can be performed by a laboratory that has met requirements equivalent to those imposed by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), as determined by the Centers for Medicare and Medicaid Services (CMS).

III. Comments on the Proposed Rule and FDA's Responses

We received over 500 comments on the proposed rule.

Some comments raised issues relating to the general provisions in subpart A of part 1271 or the registration and listing procedures in subpart B, and we considered those comments in drafting the registration final rule (66 FR 5447 at 5450, January 19, 2001). For example, in that final rule we discussed comments on dispute resolution (66 FR 5447 at 5451); homologous use (66 FR 5447 at 5458); the practice of medicine (66 FR 5447 at 5452); minimal manipulation (66 FR 5447 at 5457); the definition of "family-related allogeneic use" (66 FR 5447 at 5454); the terms "human cellular or tissue-based product" and "manufacture" (66 FR 5447 at 5455 and 5456); the regulation of bone allografts (66 FR 5447 at 5457); establishments not required to comply with part 1271 (66 FR 5447 at 5460); and the frequency of updates (66 FR 5447 at 5460 and 5461). If we considered an issue in the registration final rule, we are not reiterating our response here.

Several comments submitted to the docket for the CGTP proposed rule raised issues that are appropriately addressed in this final rule. We respond to those comments in comments 32, 48, 49, and 59, and in the discussion of § 1271.47 in section III.D.3 of this document.

We received two requests for an extension of the comment period. On April 18, 2000, a document was published in the **Federal Register** reopening the comment period for an additional 90 days (65 FR 20774).

A. General

(Comment 1) We received various comments expressing general approval of the proposed rule. One comment applauded us for addressing concerns of vital interest to the protection of the public health. Another comment expressed continued support for our efforts to design a comprehensive regulatory program for HCT/Ps, and agreed that screening and testing of donors constitutes a vital component of such a program. Other comments supported our goal of preventing the transmission of communicable diseases through donor screening and testing. One comment supported requiring semen banks to comply with the proposed screening and testing regulations.

We also received comments voicing general criticism of the proposed rule and of our comprehensive regulatory approach to cells and tissues. Some comments described the proposed rule as unnecessary or burdensome. One comment asserted that the regulations were inconsistent with the Congressionally supported "least burdensome" practice of regulation.

(Response) We acknowledge and appreciate the supportive comments. This rule contains important requirements that will help prevent the transmission of communicable diseases by HCT/Ps. Moreover, it forms a vital

component of the new tiered, risk-based regulatory program, which will be superior to the patchwork of requirements that it replaces. As discussed in greater detail in section IV of this document, this rule is consistent with Executive Order 12866, which, in its eleventh Principle of Regulation applicable to Federal rulemaking, requires FDA to "* * * tailor its regulations to impose the least burden on society * * * consistent with obtaining the regulatory objectives." FDA has designed this regulatory program to impose only appropriate, and appropriately limited, burdens.

For example, the compliance expectations for a small medical practice that provides artificial insemination are commensurate with the communicable disease risks associated with its activities. If the practice is limited to artificial insemination using either semen from an anonymous or directed reproductive donor obtained from a semen bank (§ 1271.15(d)), or semen recovered at the practice and immediately used to inseminate the donor's sexually intimate partner (§ 1271.15(e)), then the risks are minimal and the practice is not required to comply with part 1271. If the semen is not immediately transferred to a donor's sexually intimate partner but instead is stored (raising concerns about possible cross-contamination during storage), the practice would not be eligible for the exception under § 1271.15(e) and would need to comply with the requirements in part 1271 subpart B (registration and listing) and in applicable sections of subpart C (minimal standard operating procedures, minimal recordkeeping, and specific labeling for stored reproductive cells or tissue from sexually intimate partners if not screened or tested). Additional risks are associated with the recovery of semen from an anonymous or directed reproductive donor for artificial insemination; practitioners who perform these services are not eligible for the exception under § 1271.15(d) and must comply with both subpart B (registration and listing) and all of subpart C (donor screening and testing, standard operating procedures, recordkeeping, and labeling) in part 1271. FDA intends to provide further detailed guidance regarding these risk-based approaches.

We have striven to establish regulations that provide public health protection without imposing an undue burden on regulated industry. In this sense, they are also entirely consistent with the requirement for "least burdensome" regulation of devices set out in section 205(a) and (b) of the Food and Drug Administration Modernization Act of 1997.

(Comment 2) Several comments asked that provisions be made for HCT/Ps collected before the effective date of this regulation and opposed retrospective application of the new regulations.

(Response) This regulation will apply to cells and tissues recovered on or after the effective date of the regulation.

(Comment 3) One comment urged us to coordinate our donor screening requirements with those of other countries.

(Response) We support the long-term goal of international harmonization. In the process of developing this final rule, we have reviewed standards from other countries and met with representatives from the European Union, Australia, Japan, and other nations. The requirements in place in other countries are diverse and rarely static, reflecting the fact that other countries may have screening needs different from those in the United States and different tests available to them. The challenge of achieving consistency is underscored by the European Commission's announcement of the need for a new directive on human tissue, intended to replace the current myriad of 15 differing—and sometimes nonexistent—national laws on the subject. On June 19, 2002, the Commission of European Communities put forth a "Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells." Completion of this directive is expected to take several years. We applaud this effort and will continue to follow developments in tissue regulation throughout the world. However, at this time, our primary goal is to put into place the basic safeguards set out in this rule, an effort that may provide a starting point for further harmonization efforts.

(Comment 4) Several comments stated that the rule would conflict with the rule concerning privacy of health care information proposed by the Department of Health and Human Services (HHS) on November 3, 1999. The privacy rule was subsequently finalized on December 28, 2000 (65 FR 82462), and amended on August 14, 2002 (67 FR 53182).

(Response) The Department regulations on privacy of health care information (the Privacy Rule) were codified at 45 CFR parts 160 and 164. The Privacy Rule does not include the procurement or banking of organs, blood (including autologous), sperm, eyes or any other tissue or human product within the definition of health care and the establishments that perform such activities are not considered health care providers when conducting these functions (65 FR 82462 at 82477, December 28, 2000). In addition, the Privacy Rule authorizes health care providers who are subject to the Privacy Rule to "disclose protected health information to organ procurement organizations or other entities engaged in the procurement, banking or transplantation of cadaveric organs, eyes, or tissue for the purpose of facilitating organ, eye or tissue donation and transplantation" (45 CFR 164.512(h)). The preamble to the Privacy Rule notes that, when an individual has not previously authorized release of protected health information, this provision of the Privacy Rule "* * * is intended to allow covered entities [those subject to the privacy rule] to initiate contact with organ and tissue donation and transplantation organizations to facilitate transplantation of cadaveric organs, eyes, and tissues" (65 FR 82464 at 82534). The Privacy Rule further authorizes covered entities to disclose protected health information to persons subject to the jurisdiction of FDA with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity (45 CFR 164.512(b)(1)(iii)). Finally, we further note that in the event that one of the previously mentioned provisions is not applicable, covered entities may disclose protected health information pursuant to an authorization from the individual or the individual's personal representative (45 CFR 164.502(a)(1)(iv) and (g)(1), and 164.508). For these reasons, we do not believe that the Privacy Rule conflicts with this final rule.

However, FDA has considered the impact of this donor-eligibility final rule on patient privacy. We have deleted the requirement that relevant patient records accompany an HCT/P, requiring instead a summary of records. We made this change in response to concerns about privacy.

(Comment 5) One comment stated that, in the proposed rule, FDA improperly "relied" on provisions of the registration proposed rule. Another comment objected to the rulemaking process, asserting that we circumvented the usual departmental review process before publishing the proposed rule.

(Response) We disagree with both comments. In the proposed rule, the agency did not "rely" on the registration

proposed rule, but merely described another ongoing, related, rulemaking. Moreover, we made clear that the provisions of the registration proposed rule we referenced in the preamble to the donor-suitability proposed rule were merely proposals. The agency received comments related to those proposals in the donor suitability docket. When we finalized those provisions in the registration final rule, we considered comments received in the donor suitability docket, as well as in the registration docket (66 FR 5447 at 5450). With respect to the second comment, we disagree that we followed anything other than our usual review process; however, we note that these procedures constitute department practice and are not required by regulation by law or regulation.

(Comment 6) One comment cited a potential conflict with the regulation issued by CMS requiring hospitals to notify organ procurement organizations (OPOs) upon patients' death or imminent death (42 CFR 482.45). The comment pointed out that OPOs might, in some instances, determine donor eligibility for tissue donors. The comment asserted that FDA does not regulate OPOs and questioned who would be accountable for compliance with FDA regulations.

(Response) We disagree that there is a conflict between the regulations in part 1271 and CMS's regulation of OPOs; we also disagree that OPOs are exempt from FDA regulations. The determination of donor eligibility is a key function of an HCT/P manufacturing establishment. Therefore, although human organs are excluded from the definition of HCT/P, and thus not covered by the regulations in part 1271, any OPO that performs any part of any HCT/P manufacturing function, is subject to the regulations in part 1271. Such an OPO must register with the agency and comply with all applicable regulations in part 1271; thus, an OPO that screens tissue donors must do so in compliance with the regulations in part 1271 on donor screening. If an OPO performs no tissue manufacturing functions, it would not be subject to these regulations.

(Comment 7) One comment recommended that we set allowable limits for additives to allograft tissues, such as glycerol.

(Response) We decline to set a specific limit on such additives in these regulations. We point out, however, that one of the criteria in § 1271.10 for regulation of an HCT/P solely under section 361 of the PHS Act and part 1271 is that the manufacture of the HCT/P does not involve the combination of the cell or tissue component with a drug or a device, except for a sterilizing, preserving, or storage agent, and then only if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P. Should an additive raise new safety concerns or, as in the case of glycerol, be for any purpose other than sterilizing, preserving, or storage, the HCT/P would be subject to regulation under the act and/or section 351 of the PHS Act, and FDA would consider allowable limits of chemical additives in the context of the premarket review process.

(Comment 8) One comment asserted that tissue banks should audit their domestic and international tissue recovery and distribution intermediaries to assure accountability to the same standards that they themselves uphold.

(Response) We agree that documentation of these audits would help assure our goals of protecting the public health. Audits and other ways of ensuring accountability are addressed in the CGTP proposed rule.

(Comment 9) One comment supported the establishment of a central registry for tracking all reproductive tissue donors to locate donors and recipients in an emergency.

(Response) We encourage interested parties to explore methods of tracking donors, donations, and recipients, including the establishment of such a central registry. However, we do not propose to require such a registry at this time.

(Comment 10) One comment asked that the regulations clarify the responsibilities of reproductive tissue banks and client depositors with respect to length of storage of tissue and the right of a bank to destroy tissue of noncompliant depositors.

(Response) The requested clarification is beyond the scope of these regulations, which concern communicable disease transmission and not provisions of agreements between HCT/P establishments and individual clients that are unrelated to communicable disease transmission.

(Comment 11) One comment questioned why these regulations do not address the use of cellular material other than from the patient in in-vitro fertilization. Another comment supported restrictions on gene, ooplasm, and nuclear transfer.

(Response) We recognize the comments' concerns and are addressing these issues in contexts outside of this rulemaking.

B. Amendments to 21 CFR Parts 210, 211, and 820

We proposed amending §§ 210.1 and 820.1 to require manufacturers of HCT/Ps regulated as drugs, medical devices, and/or biological products to comply with the donor-eligibility procedures in subpart C and the current good tissue practice (CGTP) procedures in subpart D of part 1271. (We also proposed minor amendments, for consistency, to §§ 210.2 and 211.1.) The donor-eligibility and CGTP procedures would be considered part of CGMP requirements for drugs and the QS requirements for devices.

The proposed amendment to § 210.1 stated that failure to comply with the donor-eligibility, CGTP, or other CGMP regulations would render adulterated, under section 501(a)(2)(B) of the act, an HCT/P regulated as a drug and/or biological product, and the HCT/P, as well as the person responsible for the failure to comply, would be subject to regulatory action. The proposed amendments to § 820.1 were comparable, stating in part that the failure to comply with any applicable donor-eligibility, CGTP, or QS regulation would render a device adulterated under section 501(h) of the act.

We received no comments on the proposed amendments.

We are finalizing the proposed modifications to §§ 211.1(b) and 820.1(a), which add a cross-reference to the regulations in part 1271. As finalized, § 211.1(b) applies to HCT/Ps that are also regulated as drugs or biological products subject to the drug current good manufacturing practice (CGMP) regulations in parts 210 and 211, and § 820.1(a) applies to HCT/Ps that are also regulated as devices subject to the QS regulations in part 820.

In response to a comment submitted on the CGTP proposed rule that asserted that the "impossible to comply" language in proposed § 1271.150(c) did not provide useful guidance, we have modified this provision by replacing the "impossible to comply" language with more specific wording referring to a conflict between applicable regulations in different parts. In the event of a conflict between applicable regulations in part 1271 and regulations in parts 210, 211, or 820, the regulations specifically applicable to the product in question will supersede the more general regulations. Because the "impossible to comply" language is contained in related provisions in other parts we have made the same change to these provisions to ensure consistency. This new language is intended for

purposes of clarity. The "impossible to comply" language in our current regulations was not the subject of complaints by regulated establishments. With the revised language, FDA intends to continue to interpret the standard reasonably and does not intend to impose unreasonable burdens on establishments.

We note that the phrase "impossible to comply" has been used for products other than HCT/Ps since FDA first issued the device CGMP regulations in 1978 (43 FR 31508, July 21, 1978). Two months later, FDA used the phrase in the drug CGMP regulations (43 FR 45014, September 29, 1978). FDA explained in the preamble to the drug regulations that "impossible to comply" encompasses situations where regulations contradict or conflict each other (43 FR 45014 at 45029).

The new language on a conflict between applicable regulations replaces the phrase "impossible to comply" in §§ 210.2(a), 211.1(b), 820.1(a), and 820.1(b). (Although a revision to § 820.1(b) was not proposed, it is now necessary to revise that paragraph for consistency with § 820.1(a).) The new language pertains only to conflicts that occur between applicable regulations in one part (e.g., part 211) and applicable regulations in another part (e.g., part 1271) and not between regulations within one part (e.g., between two regulations in part 211). FDA believes that, in the event of such a conflict, the more specifically applicable regulation would be found in part 1271.

We are also finalizing proposed § 210.1(c), which would provide that the failure to comply with any applicable provision in part 1271, subparts C and D, would render a drug adulterated under section 501(a)(2)(B) of the act.

We have made minor revisions to the wording of the proposed amendments to §§ 210.1(c), 210.2, 211.1(b), and 820.1(a). These changes include the addition of a reference to section 361 of the PHS Act in §§ 210.1(c) and 820.1(a). We have also clarified in § 210.1(c) that screening refers to donor screening and that testing includes donor testing.

However, we are not finalizing proposed § 820.1(c) in this rule, which would have provided that the failure to comply with any applicable provision in part 1271, subparts C and D, would render a device adulterated under section 501(h) of the act. The act requires FDA to follow special procedures when issuing regulations under the device good manufacturing practice (GMP) authority; those procedures are not applicable to regulations issued under the CGMP authority for drugs. Before issuing regulations establishing requirements under section 520(f) of the act, the act requires FDA to submit the proposed regulations for review by an advisory committee meeting the criteria established in section 520(f)(3). However, FDA's advisory committee for device GMP regulations has not met since April 29, 1997, and only six of the required nine seats are currently filled. Although the agency believes it would be desirable to include a provision such as proposed § 820.1(c), we believe it is not absolutely necessary to the regulatory scheme. When the device GMP advisory committee has been fully reconstituted, FDA may consider submitting proposed § 820.1(c) for its consideration. In the meantime, FDA intends to enforce violations of part 1271, subparts C and D, under the enforcement provisions contained in section 368 of the PHS act (42 U.S.C. 271), and the general equitable powers of the Federal courts.

Finally, we note that the references to part 1271 in these sections (§§ 210.1, 210.2, 211.1, and 820.1) refer to "applicable" provisions of part 1271. In the event that the final CGTP rule provides that any or all provisions in that rule are not being implemented for certain HCT/Ps, those CGTP provisions would not be "applicable" for those HCT/Ps.

C. Definitions (§ 1271.3)

We have grouped all definitions pertinent to part 1271 in a single definitions section (§ 1271.3), among the general provisions of subpart A.

We received no comments on the proposed definitions of the following terms, and those definitions appear in the final rule either unchanged or with only minor changes for consistency in terminology (i.e., references to HCT/Ps): Biohazard legend (§ 1271.3(h)), blood component (§ 1271.3(i)), donor (§ 1271.3(m)), plasma dilution (§ 1271.3(p)), responsible person (§ 1271.3(t)), act (§ 1271.3(v)); PHS Act (§ 1271.3(w)); and FDA (§ 1271.3(x)). For clarity, we have added the phrase "of a cadaveric donor" to the term "physical assessment," but have made no other change to that definition (§ 1271.3(o)).

We received no comments on the proposed definitions of the terms "embryo" and "gamete," but have deleted those definitions from this final rule as unnecessary; "gamete" is not used in the codified provisions and "embryo" is generally understood. We received no comments on the term "reconstituted blood," but have deleted the term from the final rule because of its potential to cause confusion. We have incorporated the substance of the proposed definition of "summary of records" into § 1271.55 and so have deleted the definition of that term from the final rule. We received no comments on that definition. We also received no comments on the proposed definition of "quarantine," and it remains unchanged in this final rule (§ 1271.3(q)); however, comments on the quarantine provisions in § 1271.60 are addressed in section III.D.6 of this document.

1. Colloid (§ 1271.3(j)) and Crystalloid (§ 1271.3(k))

Proposed § 1271.3(k) defined "colloid," and proposed § 1271.3(l) defined "crystalloid." Both are terms used in § 1271.80 with respect to plasma dilution. Although we specifically requested comments on the appropriateness of these definitions, no comments were submitted.

For greater accuracy, we have made minor changes to the language of each definition. The final rule contains a two-part definition of "colloid" in § 1271.3(j). Under the first part, a colloid is 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. We have deleted the word "certain" from the second part of the definition, so that it now reads: "Blood components such as plasma and platelets."

The final rule replaces the word "balanced" in the proposed definition of crystalloid with "isotonic," so that the definition now refers to 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.

2. Directed Reproductive Donor (§ 1271.3(l))

The proposed rule contained a definition of "directed donor," a term used in proposed § 1271.65(b) to describe a situation in which the use of reproductive cells or tissue from an ineligible donor would not be prohibited. In considering the comments on § 1271.65(b), discussed in greater detail in section III.C.5 of this document, we concluded that, for clarity, we should limit the definition of "directed donor" to donors of reproductive cells and tissue and change the term to "directed reproductive donor." Because the term "directed reproductive donor" is used only in the context of the donation of reproductive cells and tissue, these changes do not affect the scope of the exception.

As proposed, a directed donation involved the designation of a specific potential recipient. We have maintained this part of the definition in the final rule.

(Comment 12) Our review of comments indicated that there was some confusion about whether the designation of a specific recipient could take place in the context of anonymous semen donation (i.e., a situation in which the donor and recipient do not know each other).

(Response) We did not intend for the term "directed donor" to refer to anonymous donations. Rather, our intention was to respect the existence of relationships between people. To recognize existing relationships between donors and recipients, we have added language to the definition of "directed reproductive donor" to indicate that, in a directed donation, the donor knows and is known by the recipient before donation.

We have also clarified the definition by noting that directed reproductive donors do not include sexually intimate donors, who are excepted from screening and testing requirements under § 1271.90. This change is intended to make clear that, for the purpose of this rule, there are three categories of reproductive donors, subject to three different sets of requirements listed as follows: (1) The anonymous donor, to whom all the donor-eligibility requirements apply; (2) the directed reproductive donor, whose reproductive cells and tissue may be used even if the donor is determined ineligible; and (3) the sexually intimate partner, for whom testing and screening are not required (discussed in section III.D.11 of this document).

(Comment 13) One comment requested that we define an additional category of anonymous semen donor, the "Identification Revealed Donor." Under this kind of donation, the identity of an anonymous semen donor may be revealed to the child and/or mother at some point after birth. (We also received comments supporting this type of arrangement.) The comment suggested a related change to proposed § 1271.75 so that screening for risk factors for relevant communicable diseases would not be required for donors whose identities may be revealed later.

(Response) Donor identification is outside our jurisdiction and unrelated to the purpose of this rule, which is to prevent the transmission of communicable disease. For these reasons, this rule does not address any agreements that might be entered into for revealing a donor's identity at a future time.

We note that the suggested change to the screening requirement in § 1271.75 would exempt the anonymous donors described in the comment from screening for risk factors for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human transmissible spongiform encephalopathy (TSE), including CJD and vCJD, *Treponema pallidum*, HTLV, *Chlamydia trachomatis*, and *Neisseria gonorrhea*. We cannot justify this exception on public health grounds. Whether or not the identity of an anonymous donor may be revealed later has no bearing on the appropriate screening and testing of that donor. For the prevention of the transmission of communicable disease, the same requirements should apply to all anonymous donors.

We have distinguished between directed reproductive donors and anonymous donors to respect the existence of relationships between people who know each other and have made a joint decision for the recipient to conceive a child. In contrast to the directed reproductive donor who has an existing relationship with the recipient, only the potential for a future relationship exists for the anonymous donors described in the comment. Under the identification-revealed donation arrangement described in the comment, there is no relationship between donor and recipient at the time of donation. The recipient does not even know the name of the donor at the time of the donation, and may never learn the donor's identity at all. For these reasons, we decline to add a new definition for "identification revealed donor."

3. Donor Medical History Interview (§ 1271.3(n))

The donor medical history interview is one of the relevant medical records that are reviewed in the donor screening process. We proposed to define "donor medical history interview" as a documented dialog with the donor, if living, or, if the donor is not living or is unable to participate in the interview, with an individual knowledgeable about the donor's medical history and relevant social behavior (proposed § 1271.3(o)). The proposed definition provided examples of possible interviewees and described the questions to be asked about relevant social behavior

(Comment 14) Several comments asserted that the proposed definition of donor medical history interview implies that an in-person, face-to-face interview would be required. One comment assumed that the definition includes communications with friends and life partners.

(Response) A donor medical history interview means a "documented dialog." You may conduct such a dialog in person, by telephone, or through written or other forms of communication that allow the exchange of information between interviewer and interviewee. The interview method should allow the interviewer to ask followup questions to collect necessary information or to clarify responses. In the case of a living donor, a face-to-face interview is generally the most effective way to conduct a dialog.

We agree that the definition may include communications with friends and life partners, if they are knowledgeable about the donor's medical history and relevant social behavior.

We note that the definition of "donor medical history interview" is among the provisions of this final rule that we have redrafted for clarity and plain language reasons. The meaning of the definition remains unchanged.

4. Relevant Communicable Disease Agent or Disease (§ 1271.3(r))

Proposed § 1271.3(y) contained a 2-part definition of "relevant communicable disease or disease agent." The first part listed those disease agents and diseases that are specifically identified in §§ 1271.75 and 1271.85 as relevant communicable diseases for which screening and testing would be required. These are as follows: HIV, types 1 and 2; HBV; HCV; TSE, including CJD and vCJD; *Treponema pallidum*; HTLV, types I and II; CMV; *Chlamydia trachomatis* and *Neisseria gonorrhea*. The proposed rule noted that in some instances, FDA had identified a disease agent or disease as relevant for a particular type of HCT/P and that this distinction was reflected in the proposed testing and screening requirements in §§ 1271.75 and 1271.85 (64 FR 52696 at 52701). For clarity, we have reorganized the list of identified relevant communicable disease agents and diseases in the first part of the definition (§ 1271.3(r)(1)) according to tissue type. Thus, for example, HIV, types 1 and 2, is listed as relevant for all cells and tissues; HTLV, types I and II, is listed as a cell-associated disease agent or disease relevant for viable, leukocyte-rich cells and tissues; and *Chlamydia trachomatis* is listed as a disease agent or disease of the genitourinary tract relevant for reproductive cells and tissues. This is an organizational change and not substantive.

The second part of the proposed definition described criteria for other communicable diseases or disease agents to be considered "relevant." The proposed criteria related to prevalence, transmission risk, significance of health risk, and the availability of appropriate screening and/or testing methods. We have made changes to several aspects of this part of the definition, discussed in comments 16 through 19 of this document.

"Relevant communicable disease agent or disease" is defined in the final rule at § 1271.3(r)

(Comment 15) One comment stated that we had not sufficiently demonstrated the need to expand agency oversight to include diseases in addition to HIV and hepatitis. Another comment asserted that transmission of CJD and syphilis (*Treponema pallidum*) via cornea transplants is rare or nonexistent.

(Response) When we issued part 1270 as an interim rule in 1993, among other reasons, we were acting swiftly to counter the transmission of three serious disease agents, HIV, HBV, and HCV (64 FR 52696 at 52698). One reason for the inclusion of more diseases and disease agents in the proposed rule and this final rule is that the new rules cover more types of cells and tissues than were subject to part 1270. These additional cells and tissues pose additional risks of transmitting communicable disease. For example, we are now requiring you to test donors of viable, leukocyte-rich tissue for HTLV and CMV; this requirement did not previously exist, because part 1270 did not cover such viable, leukocyte-rich HCT/Ps as semen and hematopoietic stem/progenitor cells. Similarly, we are now requiring that you test donors of reproductive tissue for *Neisseria gonorrhea* and *Chlamydia trachomatis*, a requirement that did not exist under part 1270, which did not cover reproductive tissue.

We proposed to add TSE (including CJD and vCJD) and syphilis to the list of disease agents and diseases for which donors of all types of cells and tissues would be required to undergo screening and/or testing, because these two diseases present significant health risks. We disagree with the assertion that testing is unnecessary due to the infrequency of transmission. With respect to CJD, there have been over 100 transmissions of CJD from dura mater worldwide (including 3 in the United States) and 1 transmission from cornea (in addition to 2 possible transmissions), and the number of cases of vCJD is rising. With respect to syphilis, several factors could be responsible for the lack of reports of syphilis transmission via organs, tissues, or cells, including the use of antibiotics during tissue processing and the storage of tissues at low temperature. (*Treponema pallidum* does not survive when stored at 4 °C for more than 48 to 72 hours.) However, these factors might not always be in place; i.e., antibiotics might not be used, and fresh bone grafts might not be stored under time and temperature conditions that would kill the organism, if present. Because of the potential for transmission by cells and tissue, including cornea, of both CJD and syphilis, we are maintaining the screening and testing requirements in the final rule.

(Comment 16) Several comments asked about the procedure we would use to identify additional relevant communicable disease agents and diseases under the second part of the definition. Two comments asserted that we should specify that procedure, and that, except in cases of real urgency, the agency must afford interested parties prior notice and an opportunity to comment before adding a new disease agent or disease to the list. According to these comments, providing for such input would provide the following results: (1) Reveal scientific complexities otherwise unknown to FDA, (2) allow us to avoid imposing an additional testing obligation where no test is available, and (3) help avert the unnecessary destruction of tissues in inventory. Some comments stated that tissue establishments would have a difficult time identifying a new relevant communicable disease agent or disease under the four factors set out in the proposed rule. In the absence of guidance by the agency, establishments might feel forced to conduct testing that was not supported by the risk, due to liability concerns.

(Response) We agree that public participation in these issues is important. We intend to issue guidance in accordance with the good guidance practices set out in § 10.115 to advise you when, in the agency's view, a new relevant communicable disease agent or disease exists. Good guidance practices provide the public with an opportunity to comment on guidance before its implementation, except when the agency determines that prior public participation is not feasible or appropriate (e.g., in a public health emergency). When FDA issues guidance for immediate implementation, the public is invited to comment after publication. In suitable situations, we will hold public meetings or consult with advisory committees to help us identify communicable disease agents or diseases for which donor screening and testing should be performed.

We also believe that, by issuing guidance, the agency will assist small tissue establishments, which may not be in a position to track the prevalence of emerging diseases and disease agents in a timely manner. Through guidance, FDA will perform an important communications function and assist small tissue establishments in meeting their regulatory obligations to test and screen for relevant communicable diseases and disease agents.

Under the final rule, whether or not a disease or disease agent is "relevant" under the rule will still be measured by the factors set out in § 1271.3(r)(2)(i), (r)(2)(ii), and (r)(2)(iii), taken together. We recognize that, due to a variety of circumstances, you may not be aware of every instance when a disease or disease agent meets these factors. We therefore intend to clarify the application of these criteria in guidance. FDA's role in issuing guidance is to provide notice that the definitional elements appear to be met. FDA's notification will take the form of guidance and will not constitute a rule. In an enforcement action involving testing and screening for a new relevant communicable disease or disease agent, FDA's identification in guidance of the disease or disease agent would not be dispositive of the issue of whether it meets the factors set out in § 1271.3(r)(2)(i), (r)(2)(ii), and (r)(2)(iii). In such an action, FDA would have to establish that the disease met those factors.

(Comment 17) One comment asserted that the application of "relevant" is subject to FDA's sole determination, which is further complicated by FDA's interpretation of terms such as "risk" and "appropriate screening." The comment asserted that these terms are not sufficiently defined, and that relevant risk is broadly applied and does not sufficiently address risk by specific tissue. Another comment stated that "relevant disease risk" is overly broad and would subject all tissue entities to unfair malpractice claims, leaving the system vulnerable and subject to unnecessary costs. The comment further opined that the mere hypothetical threat of a disease or agent would make it eligible for required screening and testing.

(Response) The rule establishes factors that must be met before a disease agent or disease is "relevant" under this rule. As explained in comment 16 of this document, we intend to follow good guidance practices to notify you that the agency believes additional relevant communicable disease agents or

diseases exist. This will provide the opportunity for public participation in the process.

We disagree with those comments that question the terms "relevant disease risk" and "relevant risk." These are not terms that we used in the proposed definition of relevant communicable disease agent or disease, and they do not appear in the final definition.

With respect to the comment on requiring testing and screening for a disease that poses a "mere hypothetical threat," screening and testing would be required only when supported by a sound scientific basis. Identifying a relevant communicable disease agent or disease will entail an evaluation of the risk of the disease based on the criteria in § 1271.3(r)(2). Establishments would not be required to determine independently which disease agents and diseases meet the definition of "relevant communicable disease agent or disease," and could simply follow FDA guidance concerning communicable diseases or disease agents newly identified as relevant. Establishments could also participate in FDA's identification process, for example by commenting on draft and final guidances. Such FDA guidances would identify disease agents or diseases which, in the agency's view, meet the standards for "relevant communicable disease or disease agent." Each guidance would describe effective, and thus "appropriate," screening practices, and would list recommended tests, if there are available and effective tests that have been licensed, approved, or cleared by FDA.

(Comment 18) One comment asserted that the term "prevalent" is not sufficiently defined. Another comment asked at which point and by whom a disease would be designated sufficiently prevalent among potential donors.

(Response) We have made several changes to the definition of "relevant communicable disease agent or disease" with respect to prevalence.

First, we have made the question of prevalence and/or incidence part of the evaluation of the risk of transmissibility of a communicable disease agent or disease. We have implemented this change by dividing the question of risk of transmissibility into the following two parts: (1) Is the disease or disease agent potentially transmissible by an HCT/P? and (2) does the disease or disease agent have sufficient incidence and/or prevalence to affect the potential donor population? This change is reflected in § 1271.3(r)(2)(i). Both questions are important in considering whether to require testing and/or screening for a communicable disease or disease agent; grouping them will ensure that both factors are considered together.

We believe that the factors set out in § 1271.3(r)(2)(i), (r)(2)(ii), and (r)(2)(iii) should be considered as a whole. This approach is useful in explaining the concept of prevalence/incidence. On the one hand, a highly prevalent but relatively harmless disease agent might not be considered relevant. For example, some communicable diseases (e.g., Ureaplasma urealyticum, a disease of the genitourinary tract) are prevalent, but their pathogenicity to cell and tissue recipients is of questionable clinical significance. For this reason, we do not currently consider Ureaplasma urealyticum to be a relevant communicable disease agent. On the other hand, testing or screening might be required for a less prevalent but particularly virulent agent. Examples of communicable diseases that are less prevalent, yet pose extremely significant health risks, are TSE and HIV–2.

The second change we have made is to modify the proposed language on prevalence so that it now refers to "sufficient incidence and/or prevalence to affect the potential donor population." Whereas prevalence refers to the number of existing cases over a period of time, incidence refers to the number of new cases. Both prevalence and incidence are important indicators of the risk that a potential HCT/P donor could be infected with a particular disease or disease agent, and that HCT/Ps from that donor could transmit the disease.

The third change we have made is to identify an alternative to prevalence. Under § 1271.3(r)(2)(i)(B), a relevant communicable disease or disease agent is one that "* * * either (1) has sufficient incidence and/or prevalence to affect the potential donor population, or (2) may have been released accidentally or intentionally in a manner that could place donors at risk of infection."

We intend this new language to cover both intentional and unintentional release of infectious agents. Although prevalence/incidence remains an important consideration in determining whether a communicable disease or disease agent should be considered relevant, we recognize that when an infectious agent is released, whether by accident or purposefully (e.g., to inflict harm), we may not immediately have adequate information to assess the prevalence of the disease or disease agent. In this instance, where we have information about the release of an infectious agent, and the other prongs of the definition are met, it is important for the agency to be able to respond promptly by issuing guidance on testing and screening without awaiting the accumulation of data on prevalence.

In response to the second comment, which asked at which point and by whom would a disease be designated sufficiently prevalent among potential donors, we discuss in comment 16 of this document, the procedures we will follow to communicate the agency's conclusions concerning when a disease or disease agent meets the definition of relevant communicable disease or disease agent.

(Comment 19) One comment asked us to define "significant" health risk. This comment asserted that the term is vague and subject to misinterpretation.

(Response) In response to this comment, we have replaced the phrase with more specific language in § 1271.3(r)(2)(ii). The definition now states that a relevant communicable disease agent or disease is one 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. This more specific description is modeled on language used in the agency's regulations on medical device reporting (see 21 CFR 803.3(bb)).

5. Relevant Medical Records (§ 1271.3(s))

Donor screening involves the review of relevant medical records for risk factors for, and clinical evidence of, a relevant communicable disease agents and diseases. Proposed § 1271.3(v) would define "relevant medical records" as a collection of documents that includes a current donor medical history interview and a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor. The proposed definition listed additional records that would be considered relevant medical records if they were available.

(Comment 20) One comment opposed including, in the definition of "relevant medical records," a current report of a physical assessment or examination. The comment asserted that these evaluations are of minimal utility, particularly if the available exam was not performed to look for evidence of specific disease, and suggested that the requirement be moved to the "if available" part of the definition.

(Response) We disagree with this comment. There are clear physical findings that could indicate that a donor either has a relevant communicable

disease or exhibits signs of risk factors for such a disease. Examples include jaundice, lymphadenopathy, or needle marks. The donor-eligibility draft guidance that accompanies this final rule lists physical findings that would suggest if a cadaveric or living donor could have a relevant communicable disease and that should be looked for in the physical assessment or examination.

(Comment 21) Five comments questioned the need for a physical examination of a cord blood donor. Three of these recommended that the requirement not apply to cord blood donors, but only to HCT/Ps for which the physical examination is relevant to the safety of the donor or the HCT/P. Two comments proposed requiring only a limited physical examination.

(Response) We disagree with the suggestion that it is unnecessary to conduct a physical examination of a cord blood donor. A physical examination could reveal risk factors for or the presence of a relevant communicable disease.

We note that the purpose of the physical examination is to assess for signs of a relevant communicable disease and for signs suggestive of any risk factor for a relevant communicable disease. The donor-eligibility draft guidance announced elsewhere in this **Federal Register** provides further information on physical evidence of relevant communicable diseases that may be observed during the physical examination of a living donor.

(Comment 22) One comment asserted that the scope of medical records should be limited to information pertaining to relevant communicable diseases. The comment expressed concern that a potentially significant finding would be lost in the minutiae. The comment cited autopsy results as an example of a record that does not add significant value to the donor screening process, noting also that certain products need to be released before coroner and autopsy reports are available.

(Response) We agree that the scope of medical records that you review in donor screening is limited to information pertaining to relevant communicable diseases. We disagree, however, with the assertion that autopsy results do not provide significant information. On the contrary, an autopsy can lead to the discovery of subclinical evidence of relevant communicable diseases (e.g., liver disease may indicate hepatitis). We understand that certain HCT/Ps need to be released before autopsy results are available (e.g., corneas). However, autopsy results are an important component of a donor's relevant medical records, and you must review them if they are available at the time of the donor-eligibility determination.

(Comment 23) Other comments recommended that the definition of "relevant medical records" be limited to processing records, health histories, and the infectious disease test results of the donor. These comments expressed concern that the definition includes the donor's medical records "if available." This comment urged us to make the summary of records the sole set of documents required to accompany the product.

(Response) We agree that the summary of records should be the sole set of documents required to accompany an HCT/P, and we have modified § 1271.55, as discussed in greater detail in comment 29 of this document. However, for the purposes of donor screening, we continue to believe that a larger range of information should be considered, including the donor's medical records, if available. For that reason, we have not changed the list of documents that make up the relevant medical records.

6. Urgent Medical Need (§ 1271.3(u))

Under proposed § 1271.65(b) and (c), an HCT/P from an ineligible donor could be used in cases of urgent medical need. We proposed to define "urgent medical need" as meaning that no comparable HCT/P is available and the recipient is likely to suffer serious morbidity without the product.

(Comment 24) One comment requested that we add to the definition of "urgent medical need" the requirement that the risk of morbidity with use of the product be considerably less than without the product.

(Response) We decline to make this change. We expect that doctors will use their professional judgment to balance the risk of using an HCT/P against the risk of not using it.

We have, however, modified the definition of "urgent medical need" to include the risk of death, in addition to the risk of serious morbidity. The risk of death is clearly more urgent than the risk of serious morbidity and should have been included in the proposed definition.

7. Xenotransplantation Product Recipient and Intimate Contact of a Xenotransplantation Product Recipient

Proposed § 1271.75(a)(2) would require you to determine whether a potential donor has received a xenotransplant (now called a xenotransplantation product) or has been a close contact of such a recipient. We proposed to define "xenotransplantation" and "close contact" in proposed § 1271.3(aa) and (bb).

(Comment 25) Several comments requested clarification of the definitions of "xenotransplantation" and "close contacts," including the meaning of "live cells" and "ex vivo," two terms used to define xenotransplantation. One comment preferred the term "intimate contact" to "close contact." We were also asked to provide examples of activities that could result in exchanges of bodily fluids, a factor in the proposed definition of close contact.

(Response) The final rule does not contain definitions of "xenotransplantation" or "close contact." These terms are relevant to the determination under § 1271.50, concerning whether the donor presents communicable disease risks associated with xenotransplantation. We now explain our current understanding of "xenotransplantation," "xenotransplantation product," "xenotransplantation product recipient," and "intimate contact of a xenotransplantation product recipient" in the donor-eligibility draft guidance announced elsewhere in this issue of the **Federal Register**.

The terminology used in the accompanying guidance, and the definitions provided, are consistent with guidance on xenotransplantation developed by the Public Health Service (PHS) and by FDA (PHS Guideline on Infectious Disease Issues in Xenotransplantation; Availability (66 FR 8120, January 29, 2001); Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts (67 FR 6266, February 11, 2002). In the accompanying guidance, we describe "xenotransplantation" as any procedure that involves the transplantation, implantation, or infusion into a human recipient of either of the following: (1) Live cells, tissue, or organs from a nonhuman animal source; or (2) Human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs. By "live cells" we mean cells that have the ability to metabolize or divide. By "ex vivo" we mean outside of an individual's body.

We agree with the comment that the term "intimate contact" is preferable to "close contact," because it is more specific. The donor-eligibility draft guidance describes "intimate contact of a xenotransplantation product recipient" as a person who has engaged

in activities that could result in the intimate exchange of body fluids with a xenotransplantation product recipient. Examples of intimate contacts include, but are not limited to, sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. Mere sharing of domicile or casual contact, such as hugging or kissing without the exchange of saliva, would not be interpreted as intimate contact.

D. Part 1271, Subpart C—Donor Eligibility

Subpart C of part 1271 contains the donor-eligibility requirements for HCT/Ps, including donor screening and testing.

1. General

(Comment 26) We received comments urging the use of a term other than "unsuitable" to describe a reproductive tissue donor with risk factors for relevant communicable disease.

(Response) "Suitability" is a term with wide usage in tissue and blood establishments. We understand, however, that when the term "unsuitable" is applied to a donor, it may take on an unintended meaning. For that reason, we have decided to substitute the more neutral terms "donor eligibility," "eligible donor," and "ineligible donor" throughout this final rule. Like the donor-suitability determination in the proposed rule, the donor-eligibility determination will be based on both screening and testing. A donor is "ineligible" if either screening or testing indicates the presence of a communicable disease or risk factor for a communicable disease. Throughout this rule, we refer to the "donor-suitability proposed rule," but in all other instances, even references to the provisions of that rule, we now refer to "donor eligibility."

2. What Requirements Does This Subpart Contain? (§ 1271.45)

In this final rule, we have added § 1271.45 ("What requirements does this subpart contain?"). Section 1271.45(a) states that subpart C sets out requirements for determining donor eligibility, and points out that the requirements in subpart C are a component of CGTP requirements.

Section 1271.45(b) requires a determination of eligibility, based on donor screening and testing for relevant communicable disease agents and diseases, for all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90. Section 1271.45(b) also states that, 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. We have moved this requirement from proposed § 1271.50(a). We have also extended the proposed requirement, which referred only to embryos, to cells derived from an embryo. Although this meaning was implicit in the proposed language, we have made this change for greater clarity.

Section 1271.45(c) prohibits the implantation, transplantation, infusion, or transfer of an HCT/P unless the cell or tissue donor has been determined to be eligible, except as provided under §§ 1271.60(d), 1271.65(b), and 1271.90. This was originally proposed in § 1271.50(a).

Section 1271.45(d) states that, if you are an establishment that performs any function described in subpart C, you must comply with the requirements that are applicable to that function.

3. What Procedures Must I Establish and Maintain? (§ 1271.47)

In this final rule, we have added § 1271.47 ("What procedures must I establish and maintain?"). This reflects an organizational change, but is not substantive. General requirements for establishing and maintaining procedures were proposed as part of the GTP proposed rule (§ 1271.180). These proposed requirements would apply to all significant steps in the manufacture of HCT/Ps, including donor screening and testing. However, in finalizing the donor-eligibility rule, we have decided that a separate provision on procedures specific to the donor-eligibility requirements of subpart C is warranted. To consolidate procedural requirements within the donor-eligibility requirements, and to remind you that you must develop procedures for testing and screening, we have added § 1271.47. Final section § 1271.47 is based on proposed § 1271.180, but tailored to be specific to donor-eligibility requirements. (In this final rule, we sometimes refer to procedures as standard operating procedures (SOPs).)

For greater clarity and ease of reading, we have divided the proposed language into paragraphs. Paragraph (a) of § 1271.47 requires that you establish and maintain written procedures for all steps that you perform in testing, screening, determining donor eligibility, and complying with all other requirements in subpart C. Paragraph (a) of § 1271.47 incorporates an explanation of the phrase "establish and maintain." This definition was proposed in the GTP proposed rule under § 1271.3(ll); we received no comments on the proposed definition. Paragraph (b) of § 1271.47 requires that a responsible person must review and approve all procedures before implementation. Under paragraph (c) of § 1271.47, written procedures must be readily available to personnel. Paragraph (d) of § 1271.47 contains requirements relating to departures from established procedures. Paragraph (e) of § 1271.47 states that an establishment may adopt current standard procedures, provided that certain conditions are met.

Section 1271.47 reflects the following changes to proposed § 1271.180, made in response to comments submitted to the GTP proposed rule docket:

All steps. Proposed § 1271.180 would require procedures for "all significant steps" that an establishment performs. One comment asked for examples of what constitutes a "significant step" and asked how it differs from "any step."

A "significant" step is not considered different from "any or all steps," as the latter term is used in the definition of "manufacture" in § 1271.3(e). For this reason, we have removed the word "significant," and § 1271.47(a) refers instead to "all steps."

Periodic review. Proposed § 1271.180 would require establishments to review and, if necessary, revise all procedures at least once in a 12-month period. One comment objected to the specificity of this requirement, citing the more flexible requirements in the CGMP and QS regulations.

We agree with this comment and note that the comparable requirements in the CGMP and QS regulations (§§ 211.100 and 820.40) do not require an annual review of procedures. For this reason, we are deleting the proposed requirement, § 1271.47 does not contain a requirement for an annual review of procedures.

Departures from procedures. We have replaced the term "deviation" with "departure" in this final rule to prevent confusion with HCT/P deviation reporting in the CGTP proposed rule. Several comments objected to the proposed requirement that departures from procedures be authorized in advance, because departures are not foreseeable and cannot be authorized before they occur. One comment suggested requiring a justification for the departures to be recorded at the time of the occurrence, and requiring approval of the departures by a responsible person before release of the tissue.

We agree with these comments and have modified the requirement in

accordance with the suggestion. Section 1271.47(d) now requires an establishment to record and justify any departure from a procedure relevent to preventing risks of communicable disease transmission at the time of its occurrence, rather than before. The provision further states that the establishment must not make available for distribution any HCT/P from a donor whose eligibility is determined under such a deviation unless a responsible person has determined that the departure does not increase the risk of communicable disease transmission through the use of the HCT/P.

Archiving of obsolete procedures. Proposed § 1271.180 would require obsolete procedures to be archived for at least 10 years. One comment suggested that a longer retention period of 10 years after transplantation would be more appropriate and consistent with record retention requirements in § 1271.270 (which also appear in proposed § 1271.55).

We have deleted archiving obsolete procedures as a requirement, but we recommend that establishments archive their obsolete procedures so that they may reference at any time and as needed a specific procedure used for manufacturing a specific HCT/P that is still available for use and in storage.

4. How Do I Determine Whether a Donor Is Eligible? (§ 1271.50)

Proposed § 1271.50 sets out basic requirements with respect to the donor-eligibility determination. Under proposed § 1271.50(b), the determination would be required to be performed by a responsible person. Under proposed § 1271.50(b), the responsible person would determine a donor to be eligible if the following requirements are met: (1) The results of donor screening indicated that the donor was free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases and is neither a xenotransplant recipient nor a close contact of a xenotransplant recipient, and (2) the results of donor testing for relevant communicable disease agents are negative or nonreactive.

Final § 1271.50 reflects changes in screening for xenotransplantation made in § 1271.75, discussed in comment 48 of this document.

(Comment 27) Two comments supported the provision in proposed § 1271.50 that required a determination of eligibility to be based on both screening and testing. These comments further asserted that requiring both screening and testing for all prospective donors would assure that a prospective donor who is deemed unsuitable, and who is covered by proposed § 1271.65, nevertheless, would be subject to mandatory testing.

(Response) We agree that you must base a donor-eligibility determination on both screening and testing. If the screening shows the presence of a risk factor, the donor becomes ineligible and there is no reason to conduct the testing. Thus, we disagree that testing is mandatory where screening indicates a risk factor for a relevant communicable disease and use under § 1271.65 is not sought. To require testing in the case of a donor already determined ineligible based on screening would impose an unnecessary expense.

If the screening does not reveal any risk factors, the testing should be conducted to determine the donor's eligibility. We also agree that, if donor screening indicates a risk factor, and you wish to use the HCT/P from the ineligible donor under the provisions of § 1271.65(b), you must complete all required testing.

(Comment 28) One comment asked whether a person who has tested positive for a treatable communicable disease could donate reproductive tissue.

(Response) A living donor who tests positive for a relevant communicable disease is ineligible to donate, but could become eligible to donate reproductive tissue in the future after successful treatment of the disease. In the donor-eligibility draft guidance, we make recommendations concerning the length of time following treatment of various communicable diseases after which a donor could become eligible to donate.

5. What Records Must Accompany an HCT/P After the Donor-Eligibility Determination Is Complete? (§ 1271.55)

Proposed § 1271.55(a) would require documentation of the donor-eligibility determination to accompany the HCT/P. This documentation would include a copy of the donor's relevant medical records, results of required testing, and the name and address of the establishment that made the determination. Alternatively, the HCT/P could be accompanied by a summary of records (defined in proposed § 1271.3(x)). In both instances, the donor's name must be deleted from the documentation. Proposed § 1271.55(b) would require that the establishment that generated the records used in the eligibility determination, and the establishment that made the determination, maintain the records for 10 years and make them available for FDA inspection.

(Comment 29) Several comments described as burdensome the requirement in proposed § 1271.55(a) that a copy of the donor's relevant medical records accompany an HCT/P. One comment questioned the confidentiality of information in these records, even with the donor's name redacted. Other comments urged us to require only that a summary of records accompany an HCT/P, to ensure patient privacy and the appropriate use of a patient's medical records. Another comment supported our decision to require deletion of the donor's name.

(Response) To increase confidentiality protections, we have removed the provision in § 1271.55 for relevant medical records to accompany an HCT/P. The regulation now requires only that the summary of records accompany the HCT/P. We note that this change affects only the documentation that accompanies the HCT/P; it does not affect the requirement in § 1271.75(a) to review relevant medical records.

As redrafted, § 1271.55(a) requires that, once a donor-eligibility determination has been made, the HCT/P must be accompanied by: (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 or directed reproductive donations, 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. We have specified that the distinct identification code must be affixed to the HCT/P container (rather than attached by a tie-tag) because it is crucial that this information never become separated from the HCT/P. Instead of defining "summary of records" in § 1271.3, as proposed, we describe in § 1271.55(b) that the summary of records must contain the following components: (1) A statement that the testing was performed by a laboratory certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services; (2) a listing and interpretation of the results of all communicable disease tests performed; and (3) the name and address of the establishment that made the donor-eligibility determination. We have

removed the requirement for a statement describing the types of records, which may have been reviewed as part of the relevant medical records, because it did not add useful information about the particular HCT/P. We note that the requirement to list and interpret all communicable disease tests refers not just to those tests required under this rule, but would also include any nonrequired communicable disease tests that have been performed.

We have added one item to the list of information in the summary of records, in the case of an HCT/P from a donor, ineligible based on screening, that is released under the provisions of § 1271.65(b), the summary of records must contain a statement noting the reason or reasons for the determination of ineligibility. This information will greatly assist practitioners in weighing the risks of using an HCT/P from an ineligible donor and in explaining risks to the recipient.

The final regulation, at § 1271.55(c), states that the records that accompany the HCT/P must not include the donor's name and other personal information that might identify the donor.

(Comment 30) One comment asked whether separate records would be required for all batches of HCT/Ps made from a single cell bank.

(Response) If you make multiple batches from a single cell bank, you may maintain a single set of donor-eligibility records for the cell bank. However, each HCT/P from that cell bank must be accompanied by a copy of the summary of records.

(Comment 31) One comment asserted that it is important to permit a tissue bank to qualify a donor as eligible and then to certify that eligibility to the establishment that further processes the cells or tissue without providing specific donor information. This comment also asserted that a mechanism should provide traceability through use of a donor number that can be used to trace the cells or tissue to the tissue bank if necessary.

(Response) Under § 1271.55, an HCT/P must be accompanied by a summary of records that indicates the conclusions of the donor-eligibility determination and that does not contain information that could identify the donor. We have added the requirement for 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, except in the case of autologous or directed reproductive donation, does not include an individual's name, social security number, or medical record number. This requirement is consistent with the tracking requirements of the CGTP proposed rule.

(Comment 32) One comment supported the requirement in proposed § 1271.55(b) that records regarding gamete donation be kept 10 years.

(Response) We appreciate this comment and have maintained the requirement, in § 1271.55(d), that donor-eligibility records must be maintained for 10 years.

The record retention requirements in § 1271.55(d) have been reorganized and clarified. In several instances, we have modified the requirements for consistency with the more general records requirements of the GTP rule. For example, proposed § 1271.55(b) would require records to be retained: "* * * at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product, or if the date of implantation, transplantation, infusion, or transfer is not known, then * * * at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest." Three comments submitted to the GTP docket pointed out that similar language in proposed § 1271.270(e) is confusing.

Accordingly, we have revised the relevant language in proposed § 1271.55(b) by replacing the words "implantation, transplantation, infusion, or transfer" with "administration." Section 1271.55(d) now reads "You must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest."

We have made several other changes to the record retention requirements that both improve the language and also increase consistency with the proposed GTP rule. Final § 1271.55(d) requires that all records must be accurate, indelible, and legible; this language is consistent with the proposed GTP rule (proposed § 1271.270(a)). Similarly, § 1271.55(d) sets out a more specific list of required documentation than appeared in the proposed rule; as in proposed § 1271.270(c), § 1271.55(d) specifies that you must maintain documentation of the results and interpretation of all testing and screening for relevant communicable disease and disease agents; the name and address of the testing laboratory or laboratories; documentation of the donor-eligibility determination; the name of the responsible person who made the determination; and the date of the determination. (No comments were received on either of these issues.)

We have also incorporated into § 1271.55(d) the requirement that information on the identity and relevant medical records of the donor must be in English, or, if in another language, must be translated into English. We received two comments on the docket for the GTP rule about the English language requirement in proposed § 1271.270(c). One comment stated that the proposed language implied that the original non-English record may be destroyed, and suggested revising the regulation to indicate that the original may be in any language and should be retained, but that a copy translated into English should also be kept. Another comment asserted that we should stipulate that the English translation requirement applies to products distributed within the United States.

We disagree that the proposed regulation implies that an original record that is not in English can be destroyed, and for this reason we have added the codified language that the information on the identity and relevant medical records of the donor must be retained. You must maintain the original documentation, whether or not the documentation is in English. These requirements apply to all HCT/Ps that are imported into the United States, for distribution within the United States, and that are shipped under § 1271.60(c) into the United States for processing or other manufacture before distribution in another country.

(Comment 33) One comment requested that we change proposed § 1271.55(b) to require that any party involved in the collection, processing, or transplantation of an HCT/P be allowed access to the donor's medical records.

(Response) The purpose of the language, as proposed, was to ensure FDA's access to records supporting a donor-eligibility determination. Because of concerns about maintaining the confidentiality of patient information, we decline to expand the provision to require an establishment to make medical records available to any party involved in the collection, processing, or transplantation of the HCT/P.

6. What Quarantine and Other Requirements Apply Before the Donor-Eligibility Determination Is Complete? (§ 1271.60)

Proposed § 1271.60 contained provisions for quarantine of HCT/Ps pending the donor-eligibility determination. Proposed § 1271.60(a) stated that, "* * * [f]or reproductive cells and tissues that can reliably be

stored, quarantine shall last until completion of the testing required under § 1271.85(d)." (In § 1271.85(d), we proposed to require retesting of the donor of such reproductive cells or tissue at least 6 months after the date of donation.)

(Comment 34) One comment supported the provision in § 1271.60 that permits, under certain safeguards, shipping of material that is in quarantine.

(Response) We have maintained this provision in the final rule.

(Comment 35) Many comments opposed any quarantine requirement for embryos. These comments disputed the communicable disease risks associated with embryos. They also cited increased costs from a quarantine; decreased success rates through use of frozen embryos; adverse effects on patients from a quarantine requirement; logistical concerns associated with retesting; and other possible consequences of a quarantine requirement, including loss of embryos.

Some comments asserted that current screening practices are adequate. Others asserted that FDA was interfering with the practice of medicine or criticized our approach as having a potentially negative effect on the field of reproductive medicine. Many comments suggested alternative approaches, such as optional quarantine, mandatory insurance coverage for infertility, and creation of an embryo bank. One comment described a clinically effective program using frozen embryos that was instituted to help ensure patient confidentiality.

(Response) We also received comments opposed to quarantining oocytes. Some comments distinguished between oocytes and semen based on differences in communicable disease risk, cryopreservation success, availability, cost, and other factors.

We have considered the many comments received on the retesting and quarantine requirements and have decided to clarify our intentions with respect to embryos and oocytes. In the preamble to the proposed rule, we stated that reproductive cells and tissues that can reliably be stored are those that maintain function and integrity during storage. As examples, we listed spermatozoa and sperm progenitor cells (64 FR 52696 at 52706). Given technologies at the time, we did not assert that embryos or oocytes could reliably be stored. Thus, we did not intend the quarantine and retesting requirement to apply to embryos or oocytes.

To clarify the provisions for quarantine and retesting of reproductive HCT/Ps, we have deleted the phrase "reproductive cells and tissue that can reliably be stored." The 6-month quarantine requirement in § 1271.60(a) and the retesting requirement in § 1271.85(d) applies only to anonymous semen donors.

We disagree with comments that minimize the communicable disease risks associated with reproductive cells and tissue. Among other things, these comments assert that there have been no known transmissions of disease by ova or embryos or that there is no compelling evidence to indicate that human gametes or embryos are capable of transmitting infectious disease

Each cell in the human body has receptors for viruses and bacteria and is thus capable of transmitting communicable disease. Even avascular tissue has been known to transmit disease (e.g., corneas have transmitted HBV). Semen is known to have transmitted HBV and HIV. Because embryos are a result of the combining of sperm and ova, they have the potential of being contaminated by communicable disease agents transmitted by the sperm. Moreover, bacterial contamination and transmission of HCV has occurred in assisted reproduction procedures. Two cases have been reported of women in France who were HCV antibody negative, but seroconverted after undergoing assisted reproductive technology (ART) procedures. The cause of transmission was theorized to be cross-contamination by health care workers (Lesourd, F., et al., "Transmissions of Hepatitis C Virus During the Ancillary Procedures for Assisted Conception," *Human Reproduction*, vol. 15, no. 5 pp. 1083–1085, (2000)).

Because there is a risk that ova and embryos could transmit disease, this risk should not be ignored. Given the lack of oversight and reporting requirements to date, it is difficult to know whether incidents of transmission of disease by ova or embryos have occurred.

(Comment 36) Many comments objected to the application of the quarantine and retesting requirements to directed semen donations. These comments pointed out that, under the proposed regulation, semen from a directed donor would have to be quarantined for 6 months pending retesting of the donor. Comments asserted that this would effectively bar the use of fresh semen in directed donations. Some comments cited problems with sperm cryopreservation and noted a higher conception rate with fresh semen than with frozen semen. Other comments pointed out the delay in conception that would result from quarantine. Some comments asserted that the proposed provisions would encourage people to perform inseminations without medical assistance and safety screening.

(Response) On December 14, 2001, we asked the BPAC whether, compared with fresh semen, the use of cryopreserved semen for artificial insemination reduces pregnancy rates per cycle. After a presentation of data, the committee agreed that the practice of cryopreserving semen for artificial insemination does reduce pregnancy rates.

In light of the comments and the opinion of the BPAC, we have reconsidered whether to require quarantine and retesting in directed semen donation. The requirement to retest the donor was intended to provide an important added measure of protection by addressing the "window period" between the time of infection and the presence of detectable levels of antigens and/or antibodies to communicable diseases and agents such as HIV. However, we recognize that semen from different donors varies in its ability to withstand cryopreservation. Because of the variability in whether a particular donor's sperm will survive the freeze/thaw process, a requirement for quarantine could defeat the intentions of the directed reproductive donor and intended recipient who have made a joint decision for the recipient to conceive a child. Accordingly, we have modified the regulation to except directed semen donors from the 6-month retesting requirement in § 1271.85(d). Because of this change, the requirement in § 1271.60(a) that semen be quarantined until the completion of retesting under § 1271.85(a) no longer applies to directed semen donations.

7. How Do I Store an HCT/P From a Donor Determined to Be Ineligible, and What Uses of the HCT/P Are Not Prohibited? (§ 1271.65)

Proposed § 1271.65(a) would require HCT/Ps from ineligible donors to be kept in quarantine and physically separate from other HCT/Ps until destruction or other permissible disposition was accomplished. Proposed § 1271.65(b) described three situations in which these regulations would not prohibit the use of an HCT/P from an ineligible donor, and additional requirements that would apply in those instances. The three cases were as follows: (1) Family-related, allogeneic use; (2) directed donation of reproductive cells or tissue; and (3) urgent medical need. Under proposed § 1271.65(c), the use of an HCT/P from a donor for whom the donor-eligibility

determination had not yet been completed would not have been prohibited in cases of urgent medical need. (For organizational consistency, we have moved that provision to § 1271.60 of this final regulation, which deals with HCT/Ps pending the donor-eligibility determination.) Finally, proposed § 1271.65(d) would impose special labeling requirements on HCT/Ps used under § 1271.65(b).

Proposed § 1271.65(b)(4) would prohibit making available an HCT/P from a xenotransplantation product recipient or an intimate contact of a xenotransplantation product recipient for use in the special circumstances set out elsewhere in paragraph (b) (family-related, allogeneic use; directed donation of reproductive cells or tissue; and urgent medical need). Throughout this final rule, we have adopted a more flexible approach to screening for xenotransplantation than proposed. This new approach is intended to recognize that different kinds of xenotransplantation may present different degrees of risk and to provide us with the ability to respond appropriately to these differences as the field of xenotransplantation develops. The absolute prohibition in proposed paragraph (b)(4) is not consistent with this new flexibility in approach, and so we have deleted it from § 1271.65.

(Comment 37) Several comments questioned how to comply with the requirement that HCT/Ps from ineligible donors be kept physically separate from other HCT/Ps. Some comments asserted that physical separation would require additional refrigerator storage units, presenting an unnecessary cost and space burden. These comments questioned the benefit of physically separate storage, suggested that quarantine alone should be sufficient, or requested that we delete the physical separation requirement. One comment asked whether storing in vapor phase nitrogen or encasing units in plastic bags is sufficient to prevent cross-contamination.

(Response) We have revised § 1271.65(a) to delete the requirement for physical separation. Section 1271.65(a) now incorporates language from the definition of quarantine; however, the term "quarantine" is no longer used in paragraph (a), because we believe it is more appropriately reserved for HCT/Ps awaiting the outcome of the donor-eligibility determination. Section 1271.65(a) now requires you either to store or identify HCT/Ps from ineligible donors in a physically separate area clearly identified for such use or to follow other procedures that prevent improper release, such as automated designation, until destruction of the HCT/P or other disposition in accordance with § 1271.65(b) or (c).

As revised, § 1271.65(a) now provides establishments with flexibility in achieving the goal of preventing the improper release of HCT/Ps from ineligible donors. You may choose to keep HCT/Ps from ineligible donors in a physically separate area clearly identified for such use. Such physical separation may include storage on a separate shelf in a refrigerator or freezer that also contains other shelves storing HCT/Ps in quarantine pending the donor-eligibility determination and shelves storing HCT/Ps from eligible donors. A separate refrigerator or freezer may not be necessary.

Alternatively, § 1271.65(a) allows you to use other procedures that prevent improper release. Such procedures could include automated designation to prevent improper release. For example, some establishments label HCT/Ps with bar codes and store the HCT/Ps in freezers that maintain a constant temperature. Moving the products to a separate storage area would risk transient warming. Instead, the HCT/Ps remain in the original storage area and are tracked by a validated computer system that maintains information on the results of screening and testing. At the time of release of the HCT/P, the establishment activates the computer system to assure identification and retrieval of the specific HCT/P for the intended recipient. This is an example of a system of automated designation that could satisfy the requirements of § 1271.65(a).

The provisions of the CGTP proposed rule would require you to establish and maintain procedures for the control of storage areas to prevent such problems as cross-contamination and improper release (proposed § 1271.260(a)).

As for the comment regarding vapor phase nitrogen and plastic bags, limited scientific evidence exists to show the effectiveness of measures such as overwrap bags or storage in the vapor phase of liquid nitrogen to reduce the likelihood of cross-contamination. Such measures could be used if sufficient evidence exists of their ability to minimize the risk of cross-contamination.

(Comment 38) One comment urged us to delete the exception for family-related, allogeneic use, arguing that the urgent medical need exception would apply for both related and unrelated stem/progenitor cell donors. Another comment supported the concept that hematopoietic stem/progenitor cell donors who are related to the recipient should be held to the same standards as unrelated donors with respect to screening and testing for communicable disease.

(Response) Although we recognize that the urgent medical need exception might apply in some instances of donations between family members, we decline to make the change requested by the first comment. Our intention in crafting the exception was to recognize that, in some situations, a recipient and his or her physician might weigh the risks of using an HCT/P from an ineligible family member in the absence of an urgent medical need, if such an action were in keeping with the family's wishes; this exception, with its added safeguards, would allow them to do so.

We agree with the second comment that the same screening and testing requirements should apply to donors of hematopoietic stem/progenitor cells who are related to the recipient as to unrelated donors, and the final rule is consistent with this view. However, we have chosen to defer to the family and physician the decision of whether or not to use an HCT/P from a related donor who has been determined to be ineligible. For this reason, the regulations do not prohibit such use.

We have rewritten proposed § 1271.65(b)(1) to reflect changes made in the registration final rule (66 FR 5447 at 5454). The proposed exception for "family-related, allogeneic use" extended only to first-degree blood relatives; as modified, the exception now extends to "allogeneic use in a first-degree or second-degree blood relative." Our decision, expressed in the registration final rule, to broaden the scope of related donors was based on several factors, which also apply here. The likelihood of finding a donor with a haplotype identical to that of the recipient is greater among blood-related individuals than among unrelated individuals. In addition, for certain ethnic groups, it is extremely difficult to find an appropriate unrelated donor. Finally, registry outcome data for some hematologic malignancies suggest that peripheral blood and bone marrow transplant recipients may have a better survival rate when transplanted with hematopoietic stem/progenitor cells from related donors (66 FR 5447 at 5454).

Parents, children, and siblings are considered first-degree relatives. Aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren are second-degree relatives. Relations by adoption or marriage are excluded from § 1271.65(b)(1), because they are not in the same genetic pool as blood relatives.

(Comment 39) We received comments on the proposed provision for directed

donation of HCT/Ps from ineligible donors. Elsewhere in this rule, we respond to comments on the definition of directed reproductive donor and on the applicability of retesting requirements to directed donations of reproductive cells and tissues.

One comment on proposed § 1271.65 praised the directed donor provision as appropriate. This comment stated that the directed donor provisions should also apply when a woman seeks a second child by the same anonymous donor with known high-risk behavior.

(Response) We disagree that the directed reproductive donor provisions of § 1271.65(b) extend to anonymous donation. As discussed in comment 13 of this document, the term "directed reproductive donor" does not apply to anonymous donations, but to situations where the donor knows, and is known by, the recipient. Moreover, under this final rule, all potential anonymous semen donors must be screened for risk factors for relevant communicable disease, including high-risk behavior; potential donors with a high-risk behavior will be determined ineligible.

(Comment 40) One comment expressed concern about allowing patients and physicians to decide whether to use donated gametes from a directed reproductive donor who is found to be ineligible. This comment asserted that it is essential that patients be fully informed, and that written contracts be signed indicating the possible risks to recipient and baby, so that there is complete understanding for the risks involved.

(Response) It is essential that the patient who chooses to use a directed donation from an ineligible donor be fully informed of the risks involved. For any use under § 1271.65(b)(1), the establishment must notify the physician using the HCT/P from the ineligible donor of the results of testing and screening. Under § 1271.65(b), the HCT/P must be labeled prominently with the Biohazard legend and must bear 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)." In the case of reproductive HCT/Ps, this includes risk to the baby. We have removed the proposed requirement for the establishment to document that the physician agreed to explain the communicable disease risks associated with the use of the HCT/P to the recipient or the recipient's legally authorized representative and that the physician agreed to obtain from the recipient or the recipient's legally authorized representative consent to use the HCT/P. We decline to require a written contract between physician and patient. We know that physicians are under legal and ethical restrictions, requiring them to discuss the risks of communicable disease transmission stemming from the use of HCT/Ps. We rely on physicians to meet these obligations when obtaining consent to procedures involving HCT/Ps from patients and their legal representatives.

(Comment 41) One comment on directed donations of reproductive cells or tissue praised FDA for adding clarity to a process that has created confusion for donors and patients. This comment endorsed the procedures in proposed § 1271.65(b), but objected to the proposed requirement for physician consent. The comment asserted that the patient has the right to make his or her own decisions about medical treatment, that physician consent is unnecessary because of other standards of physician conduct, and that some physicians may withhold consent for invalid reasons.

(Response) In light of this comment, we have reconsidered the necessity of requiring documentation of the physician's authorization of the use of an HCT/P from an ineligible donor in the directed reproductive donor situation, as well as in cases of urgent medical need or use in a first- or second-degree blood relative. Our decision is not based on an evaluation of patients' rights, but on the observation that, in each of these situations, a physician will be closely involved in the decision to use the HCT/P from the ineligible donor. For this reason, no additional requirement to obtain physician consent is necessary.

For the same reasons, we have also removed the requirement for physician authorization from the provisions governing use of an HCT/P for urgent medical need before completion of the donor-eligibility determination (§ 1271.60(d)).

(Comment 42) Several comments strongly supported the urgent medical need provision in proposed § 1271.65(b) and (c). Some comments commended the structuring of the proposed regulations, noting that the transplanting physician and the informed patient may deem appropriate a tissue that is positive for infectious disease when comparing alternatives, particularly in a matter of life or death or other emergency medical situations. One comment asserted that the transplant physician must be the ultimate authority for the use of tissues from all donors and noted that the prevalence of CMV positivity in the normal donor population will make this exception widely used.

(Response) We have maintained the provisions for urgent medical need, although, as noted, the provisions governing use pending the donor-eligibility determination have been moved to § 1271.60. (To ensure that the physician receives sufficient information about the risks of the HCT/P, § 1271.60(d)(2) requires that an HCT/P from a donor for whom the eligibility determination is not complete be accompanied by results of donor screening and testing that have been completed, as well as a list of any screening or testing that has not yet been completed.)

We also note that, under the final regulation, you are not required to determine a donor ineligible on the basis of a reactive CMV test, but under § 1271.85(b)(2) you must establish and maintain an SOP governing the release of an HCT/P from a donor whose specimen tests reactive for CMV. Thus, it will be unnecessary to invoke the urgent medical need provisions to use an HCT/P from a donor who has tested positive for CMV. (See the discussion in comment 60 of this document.)

(Comment 43) One comment asserted that labeling tissue "untested for Biohazard" might cause transportation issues, because commercial carriers are reluctant to transport a container labeled "Biohazard." The comment recommended that the proposed regulations clarify that the tissue container, not necessarily the tissue transport container, be labeled "untested for Biohazard."

(Response) The labeling requirements in this final regulation apply to the labeling of the HCT/P. (An HCT/P made available under § 1271.60(d) must be labeled "NOT EVALUATED FOR INFECTIOUS SUBSTANCES," and an HCT/P made available under § 1271.65(b) must bear the Biohazard legend; in both instances, the label must state: "WARNING: Advise patient of communicable disease risks.") Other regulations, e.g., those issued by the Department of Transportation, may apply to the shipping container.

8. How Do I Screen a Donor? (§ 1271.75)

Proposed § 1271.75(a) would require screening of all donors, except as provided in § 1271.90, for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, including, at a minimum, HIV, HBV, HCV, and TSE, including CJD and vCJD. Under proposed § 1271.75(b), donors of reproductive cells or tissue would be screened for genitourinary diseases that can be transmitted with

the recovery of reproductive cells or tissues, including at a minimum *Chlamydia trachomatis* and *Neisseria gonorrhea*. Under proposed § 1271.75(c), donors would also be screened for xenotransplantation or close contact with a xenotransplantation product recipient. And proposed § 1271.75(d) would allow establishments to follow an abbreviated donor screening procedure when a complete donor screening had been performed within the previous 6 months.

We have deleted the phrase "at a minimum" from § 1271.75(a) and (b), because it might give the impression that screening is required only for those relevant communicable diseases listed in § 1271.75. Although at this time we only require screening for those listed diseases, additional diseases may be identified as relevant in the future. As discussed in comment 16 of this document, we intend to issue guidance that notifies you when we have identified additional relevant communicable diseases that appear to meet the definition in § 1271.3(r)(2).

Section 1271.75, as finalized, requires the establishment that performs donor screening to review the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases. For consistency with testing requirements, we have added the requirements that you screen all donors for *Treponema pallidum* (§ 1271.75(a)(1)) and that you screen donors of viable, leukocyte-rich cells or tissue for relevant cell-associated communicable diseases, including HTLV (§ 1271.75(b)). These additional screening requirements impose only a minimal burden. We describe screening factors for these relevant communicable diseases in the donor-eligibility draft guidance.

(Comment 44) Proposed § 1271.75(a)(1) would require screening of all donors for human TSE, including CJD. We received several comments on this provision. One comment supported the proposed screening requirements as written. Another comment stated that the agency should make clear whether it intends procurers of human tissue to apply the policies in the draft guidance for blood donors issued on November 23, 1999. Other comments argued that semen and oocytes should be exempt from screening for TSE, or questioned why the screening is applied to all donors, not just donors of dura mater or cornea. One comment expressed concern that particular symptoms of TSE, such as changes in speech or gait, are not specific to TSE.

(Response) Given the severity of TSE, the lack of an approved test, and the lack of information about the tissue distribution of the vCJD agent in humans, we continue to believe that it is necessary to screen all prospective donors for risk factors. In January 2001, we asked the TSEAC to evaluate the risk of transmission of vCJD through the transplantation, implantation, infusion, or transfer of HCT/Ps. The committee agreed that, compared to the risk of transmission of vCJD by blood transfusion, there is a significant risk of transmission of vCJD from HCT/Ps.

We recognize that the potential for transmission appears to differ between different types of HCT/Ps, with the greatest risk associated with corneas and dura mater. Nevertheless, you must screen all donors for TSE, for the previously listed reasons. This screening would include questions about risk factors for sporadic CJD and vCJD, and donors would be subject to exclusion based on those factors. We also recognize that some TSE symptoms are not specific to TSE. The specific symptoms to watch for are discussed in the CJD draft guidance.

(Comment 45) The proposed regulations did not contain an exception from the donor medical history interview for corneas procured under legislative consent; i.e., in accordance with a State law that allows the medical examiner or coroner to procure corneal tissue without the consent of the donor's next of kin. The preamble to the proposed rule stated that requiring a donor medical history interview for corneas obtained under legislative consent is necessary to ensure that the risk of communicable disease transmission is appropriately assessed. We noted that the necessity of adequate screening for TSE illustrates the importance of the donor medical history interview (64 FR 52696 at 52703).

We also noted that the proposed definition of donor medical history interview would permit the interview to be conducted with an individual knowledgeable about the donor's medical history and relevant social behavior (e.g., primary treating physician) and would not require an interview with the next of kin. For this reason, we considered that the proposed regulation and State laws on legislative consent may coexist and stated that we did not intend to preempt those laws. We specifically requested comments on any potential conflicts that might make it impossible to comply with both this regulation and State laws on legislative consent.

We received many comments about the proposed requirement for a donor medical history interview. Most of these comments came from eye banks.

Comments from eye banks that supported the proposal described their positive experiences performing medical history interviews. One comment described a next-of-kin interview that revealed the information that the potential donor's sister had died from CJD, information that would not have otherwise been obtained. Another comment supported the interview as a means of detecting high-risk behavior for diseases other than CJD, such as hepatitis and HIV, and said that FDA should carefully consider any interview questions relating to TSE with input from transplant practitioners and other experts. Several comments cited the risk to patients if donors are not screened with an interview. One comment from the medical director of an Italian eye bank described a positive experience with a recently implemented Italian requirement to obtain medical and social information through an interview.

Some comments criticized the recovery of corneas under legislative consent, asserting that autopsy reports are insufficient for assessing high-risk behaviors and that donors from medical examiner's or coroner's offices have an increased likelihood of high risk behavior. One comment asserted that, although part of the justification for legislative consent has been that there is a cornea shortage in this country, current donation rates have enabled most eye banks to become exporters.

Most comments on this issue opposed a requirement for a donor medical history interview for all cornea donors. One comment opposed the requirement but appreciated FDA's efforts to help ensure a safe supply of donor corneal tissues. Another comment asserted that the government should stay out of eye banking.

Many comments cited benefits of medical examiner laws, and some comments expressed the view that the proposed requirement would eliminate the procurement of corneas under legislative consent. Some expressed concern about diminished cornea supplies. Others asserted that the time required for screening would detract from cornea viability and quality, and some comments expressed concern about decreased access to healthy young corneal material from the medical examiner donor pool. Numerous comments cited the added expense of performing a medical history interview.

Many comments asserted that additional screening is unnecessary, or disputed the usefulness of an interview. Two comments asserted that the medical/social histories performed on

all cases obtained under legislative consent are just as comprehensive as those obtained with a next-of-kin consent and a medical/social history questionnaire. Other comments expressed doubt that the interview would be effective in screening for CJD or would increase the safety of corneal tissue.

Many comments disputed the risk of CJD transmission via corneas. One comment asserted that TSE cases are not brought to the medical examiner's office for determination of cause of death. Another comment asserted that there is no evidence of any increased risk of disease transmission through corneas obtained under legislative consent absent a medical history interview and that mandating an interview does not appear to have adequate scientific substantiation. Another comment stated that CJD is not sufficiently prevalent to warrant testing and screening.

The Eye Bank Association of America (EBAA) commissioned a report, which it submitted to the docket, on the occurrence and transmissibility of CJD as it relates to cornea transplantation. The report concluded, in part, that screening for symptoms of CJD would have minimal impact on safety but would reduce the supply of donor corneas. One comment objected to the report's conclusion and supported a medical/social history interview. On the other hand, one comment indicated that, based on the EBAA report, it now recommended that the regulation permit corneal donation under legislative consent without a donor medical history interview.

(Response) We have carefully considered the many comments on this difficult issue. Since the publication of the proposed rule, our concerns about preventing the spread of TSE, including vCJD, have increased. We have taken steps to address those concerns by developing an agency action plan and issuing new guidance documents, including guidance specific to HCT/Ps. In August 2001, HHS also announced a TSE action plan. One of FDA's responsibilities under the departmental action plan is to review and upgrade our policies designed to prevent potential exposure to TSE through blood transfusion or tissue transplantation or transmission of TSE through FDA-regulated products. (You can find information about the departmental action plan on the Internet at *http://www.hhs.gov/news/press/2001pres/20010823.html.*)

We developed our action plan for TSE in April 2001. The plan has several focus areas, including prevention of exposure to TSE through human and animal products, blood transfusion, tissue transplantation, and other FDA-regulated products. FDA also wants to establish a coordinated education and outreach program to the community, and to expand research in TSE. The plan will enhance regulatory tools, and help enforce regulations concerning cattle feeding and import restrictions. The action plan is posted on the Internet at *http://www.fda.gov/oc/oca/roundtable/bse/FDA_actionplan.html.*

Another example of FDA's heightened concern with potential TSE transmission is the publication of the guidance entitled "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products (January 2002)," available on the Internet at *http://www.fda.gov/cber/gdlns/cjdvcjd.pdf.* This guidance recommends blood donor deferrals for travel to the UK and the rest of Europe, for military personnel who resided in U.S. military bases in Europe, and for receipt of blood in the UK.

In January 2001, we asked the TSEAC to evaluate the risk of transmission of vCJD through the transplantation, implantation, infusion, or transfer of HCT/Ps and to compare this risk to that of the transfusion of blood and blood products, for which precautionary measures have already been adopted. We specifically requested advice on how information about residence/travel history could best be obtained and noted the relevance of this question to corneas procured under legislative consent. The committee agreed that, compared with blood transfusion, there is a significant risk of transmission of vCJD from HCT/Ps, and noted that dura mater and cornea have the greatest risk. A majority of the committee supported deferral for donors of dura mater and cornea who had possibly been exposed to the bovine spongiform encephalopathy agent, but the committee did not vote on the question of whether an interview should be required of all donors.

Since that meeting of the TSEAC, we have issued a draft guidance document entitled "Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated June 2002, available on the Internet at *http://www.fda.gov/cber/gdlns/cjdvcjd0602.pdf.* This draft guidance document contains our current recommendations on appropriate donor screening measures for CJD and vCJD. This draft guidance was discussed at the TSEAC meeting in June 2002.

It would be inconsistent with our level of concern about TSE to fail to require a donor medical history interview for some corneas, when it is generally agreed that corneas are among the tissues most likely to transmit TSE. The information needed to screen for TSE (e.g., cognitive changes; travel history) is not the sort that can be obtained through an autopsy or through a review of investigators' reports or hospital charts.

Moreover, although the preamble to the proposed rule used TSE to illustrate the need for a medical history interview for all cornea donors, questions pertaining to other relevant communicable diseases would also go unanswered without an interview. We agree with the comment that supported the interview as a way of screening for diseases other than CJD, such as hepatitis and HIV.

The EBAA report focused on CJD, and not on other diseases that might be screened for, including HIV. The report recommended against requiring a donor medical history interview in cases of legislative consent. In reaching this conclusion, the report's authors made certain assumptions about the diagnosis, course, and prevalence of CJD in the cornea donor population, including the frequency of misdiagnosis of CJD. As we discuss in this document, varying these assumptions can lead to very different conclusions. Moreover, the report analyzed the possible effect of supplemental screening applicable to all cornea donors, assuming a new screening requirement where none currently exists. However, the requirement for a donor medical history interview is currently in place with respect to all cornea donations except for the small percentage obtained under legislative consent. (The actual percentage of cornea donations obtained under legislative consent is unknown. The EBAA report used an unsupported value of 10 percent.)

In evaluating the proposed regulation, the EBAA report considered the number of potential cornea donors who might be deferred for CJD risk because of the results of supplemental screening but who in fact do not have CJD (i.e., the number of all cornea donors who might be erroneously excluded). Depending on the assumptions made, the estimated number of cornea donors with CJD and the number of donors erroneously excluded by screening could vary tremendously. For instance, the authors of the report assumed that 1 percent of actual CJD cases would be missed, and

diagnosed as some other neurological disease. They calculated that it would take 8.1 years of screening to exclude one actual case of CJD, and the numbers of otherwise eligible donors incorrectly excluded by screening would range from 18,415 to 73,362 (depending upon the specificity of the screening questions). If, instead of 1 percent, we make the assumption that 10 percent of cases of CJD would be misdiagnosed, then it would take 1.4 years of screening to exclude 1 actual case of CJD, with 3,219 to 12,876 donors incorrectly excluded. Thus, the assumption made by the authors resulted in a calculation of approximately six times the number of donors incorrectly excluded as under another possible scenario. Furthermore, the EBAA model estimates the numbers of incorrectly excluded donors that would result assuming that the additional screening would apply to all cornea donors. However, the additional screening required under this rule would affect only the subset of donors from whom an interview is not currently obtained (e.g., corneas obtained under legislative consent).

Because the report failed to explicitly consider a variety of uncertainties in the model assumptions, did not consider the effect of the donor medical history interview requirement on the appropriate subset of potential donors, and did not include diseases other than CJD in the risk assessment, we decline to follow any recommendation based on the results.

We disagree with comments that predict a shortage of corneas resulting from this rule. At present, approximately 30 percent of corneas recovered in the United States are exported (2002 Eye Banking Statistical Report, Eye Bank Association of America). Because any estimates of potential reductions in donations under legislative consent are quite speculative, we have not included such estimates in this response. Even if this final rule led to a reduction in donations under legislative consent, we do not anticipate that a shortage would result.

(Comment 46) Although comments expressed concern about the effect of the proposed requirement for a donor medical history interview on medical examiner laws, we received only a few responses to our request for comments on any potential conflicts that might make it impossible to comply with both this regulation and State laws on legislative consent. One comment agreed with requiring a donor medical history interview, but noted that, given privacy considerations, an interview with a primary treating physician may be difficult to obtain without permission of the deceased and/or the deceased's family. Another comment asserted that, for the proposed rule not to conflict with State laws on legislative consent, it would have to allow the medical examiner or pathologist who performs the autopsy to qualify as an "individual knowledgeable about the donor's medical history and relevant social behavior" and to respond to a modified set of history questions appropriate to the medical examination. According to the comment, other medical and social history would be obtained through the case file containing investigator's reports, hospital charts, or other sources of donor history.

(Response) As discussed in section VI of this document, we contacted the States to give them the opportunity to comment on any possible preemption issues. No States replied to our request.

In this final rule, we have defined "donor medical history interview" as a documented dialog 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. If the donor is not living or able to participate in the interview, the interview must take place with an individual or individuals who are able to provide the information sought in the interview. (This language replaces "individual knowledgeable about the donor's medical history and relevant social behavior" from the proposed rule. This change is for purposes of clarity and plain language, and it does not affect the definition's meaning.) Examples of these individuals who could possibly provide the appropriate information include the donor's next-of-kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, or the primary treating physician.

We continue to believe that the definition of "donor medical history interview" provides sufficient flexibility to allow for the continued recovery of corneas under legislative consent. However, we recognize that there may be some difficulty in communicating with the primary treating physician without obtaining permission from the deceased and/or the family of the deceased, and that therefore this final rule may have an effect on the ability of medical examiners and coroners to recover corneas under State legislative consent laws. But, given the known transmission by corneas of HBV and CJD, and the potential for corneas to transmit other communicable diseases, including TSE, we have concluded that making an exception from the requirement for a donor medical history interview in the case of corneas obtained under legislative consent is not justified.

We disagree with the comment that urged us to interpret the definition to include an interview with the medical examiner or pathologist who performs the autopsy. Although the medical examiner or pathologist will have useful clinical information that should bear on the donor-eligibility determination, it is unlikely that this person will know the donor well enough to answer questions about his or her medical history, travel history, and/or social behavior. Therefore, an interview with the medical examiner or pathologist would be inadequate to fulfill the interview requirements.

(Comment 47) In the preamble to the proposed rule, we noted that, together with CDC, we were reviewing the risk factors for transmission of relevant communicable diseases in light of current scientific knowledge. Based on that review, we planned to specifically describe, in a guidance document, risk factors and screening information to assist establishments in complying with the regulations (64 FR 52696 at 52703). Although the proposed rule did not specify risk factors, we received many comments opposed to a screening factor that would prevent men who have had sex with men from donating semen anonymously. (Many comments also focused on the proposed requirement to quarantine directed donations of reproductive cells and tissue. As discussed in comment 36 of this document, we have deleted this requirement from this final rule. The final regulations allow the use of fresh semen from directed reproductive donors.)

Some comments disagreed with considering homosexual men to be "high risk donors" and disputed the scientific basis for excluding these men as donors. Many comments cited the efficacy of the blood test for HIV, with retesting after a 6-month quarantine, although one comment noted that HIV antibody testing is imperfect. Many comments disputed the public health benefits of the rule, although some applauded the agency for trying to craft safeguards to protect the public.

Other comments asserted that the regulations would abridge the reproductive, civil, or constitutional rights of both donor and recipient, but did not provide an explanation of the scope of those rights or a legal analysis of how this rule would affect them. Many comments argued that the proposed regulations were discriminatory. Some comments

suggested language for the donor-eligibility draft guidance.

(Response) In response to the comments suggesting that FDA should allow establishments to rely on HIV test results alone, or on quarantine and retesting, without screening for risk factors, FDA rejects that approach at this time. Although it is reasonable to expect that more sensitive nucleic acid amplification testing (NAT) will be available soon for reproductive tissue donors, even that testing may fail to detect early stage HIV and other infections, particularly because the level of viremia may be extremely low in the early stages of infection (Refs. 1, 2, and 3). Moreover, even the best test may fail to provide an accurate test result due to human error in running the test or in linking the test result to the correct donor. Accordingly, FDA believes that, based on the current state of testing and current knowledge about disease transmission, it is necessary to screen for risk factors as well as to test for diseases such as HIV.

Like the proposed rule, this final rule does not specify risk factors. Risk factors and other information about screening are contained in the donor-eligibility draft guidance announced elsewhere in this **Federal Register**. We welcome comments on the guidance document.

In developing the guidance, we have seriously considered the comments. To obtain up-to-date information on risk factors, we have worked with CDC. CDC performed a literature search and then, on June 26 and 27, 2000, held a donor suitability consultation to consider whether the 1994 "Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs" (*Morbidity and Mortality Weekly Report* 1994; 43(RR–8)), should be revised with respect to men who have sex with men.

Approximately 50 persons were invited as consultants. They represented transfusion and transplant professional organizations, public health experts, donor families, persons receiving transplants, ethicists, and donor rights advocates. Representatives of the Department of Health and Human Services and its component agencies also participated. Observers at the meeting were also encouraged to contribute.

Representatives of CDC presented the scientific literature search prepared as a background for the consultation. Presenters compared the transmissibility of infection through blood, organs, tissues, and reproductive tissues. Data were presented on the incidence and prevalence on HIV, HBV, and HCV for specific groups and risk behaviors; these data were derived primarily from the literature published between 1995 and 2000 and from unpublished sources. Data indicated that, compared to the general population, the incidence and prevalence rates for HIV, HBV, and HCV were substantially higher for heterosexuals attending sexually transmitted disease clinics, men who have sex with men, commercial sex workers, and injection drug users.

After the consultation, it was concluded that there is no new data that would warrant revising the 1994 guidelines. CDC and others also concluded that current data are not sufficient to allow the identification of lower-risk subsets of currently excluded population groups, and thus, to refine the exclusionary criteria. At the consultation, representatives of CDC encouraged the development of new data.

On December 14, 2001, we asked the Center for Biologics Evaluation and Research's (CBER) BPAC, whether there are existing data that identify subsets of men who have had sex with other men in which the incidence and prevalence rates for HIV, HBV, and HCV of the subsets are similar to the population at large. By a 10 to 0 vote, the committee advised that these data do not exist.

We have reviewed relevant legal authorities and disagree that these regulations discriminate or improperly abridge donor or recipient rights. We further note that, since FDA has tailored the rule's requirements to take into account an existing relationship between a donor and recipient (for example, FDA has not required quarantine and retesting for directed reproductive donors, permits the use of reproductive tissue from ineligible directed reproductive donors, and requires no testing for sexually intimate partners), the comments' remaining objections relate almost exclusively to anonymous donations of reproductive tissue. We will continue to examine the data on risk factors and, as new data are developed that justify changes to our guidance, we will make those changes in accordance with good guidance practice.

(Comment 48) Proposed § 1271.75(a)(2) would require screening a potential donor to determine if he or she had received a "xenotransplant" or was a "close contact" of a xenotransplant recipient. Two comments agreed that xenotransplantation recipients should be deferred as tissue donors, but asserted that close contacts do not need to be deferred. One comment asserted that there have been no reports of the spread of zoonoses to close contacts or household members. The comment further recommended use of a simplified question in donor screening.

(Response) This final rule adopts a different approach to screening for xenotransplantation than proposed. The rule is intended to permit the agency added flexibility in responding appropriately to the risks presented by different kinds of xenotransplantation as this field develops and changes. To this end, we have modified several provisions of the final rule with respect to xenotransplantation, including the screening requirements set out in § 1271.75. (Changes to the definitions and to § 1271.65 are discussed in comment 25 and the text before comment 37 of this document.)

The final rule requires screening for "communicable disease risks associated with xenotransplantation." The donor-eligibility draft guidance that accompanies this final rule describes those risks. Because, at this time, so few xenotransplantations have been performed, and much is unknown about the actual risks of xenotransplantation, the risks for which you must screen may be potential or hypothetical risks. We currently consider both the xenotransplantation product recipient and the intimate contact of a xenotransplantation product recipient to be at risk for acquiring zoonoses, and, as in the proposed rule, these individuals would be ineligible to donate HCT/Ps. However, if requested to do so through a request for an exemption from or alternative to the regulations under proposed § 1271.155 when finalized, we will consider exceptions for certain ex vivo exposures (e.g., exposure to a well-characterized cell line, or exposure across a physical barrier).

We have considered the comments' assertion that intimate contacts should be eligible for donation, based on the lack of reports of zoonosis spread, and we disagree. Given the potential risks associated with the spread of diseases from live animal cells, tissues, and organs, we believe that the most prudent course at this time is to defer intimate contacts, and the donor-eligibility draft guidance follows this course. As with hepatitis and HIV, those individuals most likely to be infected by a xenotransplantation product recipient with a zoonosis are the recipient's intimate contacts. Should that individual become infected with a zoonosis, then an HCT/P from that intimate contact could transmit the zoonosis to the recipient of that HCT/P.

The donor-eligibility draft guidance describes the types of questions that can

elicit information on communicable disease risks associated with xenotransplantation. We welcome comments on the draft guidance.

(Comment 49) One comment said that, instead of questioning at the time of donation, FDA should require that past xenotransplantation product recipients and their next of kin be notified by the medical institution performing the clinical trials that they are deferred from donating blood and tissues.

(Response) We agree that a transplant institution should tell a xenotransplantation product recipient not to donate blood and tissues (e.g., as part of informed consent). The PHS Guideline on Infectious Disease Issues in Xenotransplantation (January 19, 2001) recommends that xenotransplantation product recipients be instructed not to donate blood, blood components, tissues, breast milk, ova, sperm, or any other body parts for use in humans. This document further recommends that the recipient inform his contacts (now referred to as "intimate contacts") not to donate.

However, as an added precaution, an HCT/P donor, or other person interviewed in the donor medical history interview, should be questioned at the time of HCT/P donation. Unless prodded by the question, the donor may not remember that he or she is not supposed to donate HCT/Ps. Moreover, another person interviewed in the donor medical history interview may not remember the warning against donation unless specifically asked about xenotransplantation.

(Comment 50) Proposed § 1271.75(d) would allow an abbreviated donor screening procedure for living donors, as long as complete donor screening is performed every 6 months. One comment asserted that it is impractical to conduct abbreviated screening at each donation for anonymous semen donors and that a complete donor-eligibility determination every 6 months is unnecessary. Another comment recommended that a complete screening be recorded with each donation event. A third comment asked us to revise the regulation to indicate that an abbreviated donor screening would not be acceptable if there has been a change in screening requirements since the last complete screening procedure was performed on the donor.

(Response) We decline to make the changes suggested by the comments. We believe that the requirement for a complete screening procedure (i.e., a donor medical history interview), review of medical records and physical examination, every 6 months is appropriate because in this timeframe a potential donor may develop physical signs of a communicable disease that can be detected by examination.

With an abbreviated screening procedure, a full review of records is not necessary, but you must make sure that there have been no changes in a donor's risk factors, including high risk behavior, since the previous donation. You may accomplish this by having the donor read a written list of risk behaviors and asking whether he or she has participated in these behaviors.

With respect to changes in screening requirements, we agree with the intent of the comment but disagree that the requested change is necessary. Information on screening (e.g., risk factors) is contained in guidance that, although not binding, represents our current thinking on the topic. If FDA guidance on screening has changed since the last donation (for example, if a new risk factor has been added), we recommend that you screen in accordance with the new guidance at the next scheduled donation following the implementation date of the guidance (for example, by screening for the new risk factor).

We have made several changes to the regulation for clarity. We have replaced the phrase "on subsequent donations" with "on repeat donations" to clarify that we intend this abbreviated procedure to apply in repeat donation situations (e.g., semen).

We note that while § 1271.75(d) addresses abbreviated screening procedures for repeat donors, the requirements for quarantine, testing, and retesting applicable to repeat donations are contained in §§ 1271.60, 1271.80, and 1271.85. In comment 53 of this document, we discuss changes to the testing requirements applicable in the repeat donor situation.

9. What Are the General Requirements for Donor Testing? (§ 1271.80)

Proposed § 1271.80 would require an establishment to test donor specimens for relevant communicable disease agents, to adequately and appropriately reduce the risk of transmission of relevant communicable diseases. Among other things, proposed § 1271.80 sets out requirements for the timing of specimen collection; the use of FDA-licensed, approved, or cleared tests; which laboratories could perform the required tests; exceptions applicable to certain test results for CMV or syphilis; and determining the adequacy of a specimen where the donor has received a transfusion or infusion.

a. *Testing of mother.* Proposed § 1271.80(a) stated that, in the case of a fetal or neonatal donor, a specimen from the mother is generally acceptable for testing.

(Comment 51) One comment emphasized the importance of permitting testing of an appropriate specimen from the mother of a fetal or neonatal donor. Another comment requested that we require maternal tests to be validated as predictive of transmissibility of infection in the fetal or neonatal tissue.

(Response) We have reexamined the proposed language on maternal testing and now believe that testing of the mother is preferable to testing of the fetal or neonatal donor. We are particularly concerned about the possibility that HBV might be transmitted at or around the time of birth, or possibly in utero. In such cases, HBV testing of the fetus or neonate could lead to a false negative result, but testing of the mother would be positive. We have therefore revised § 1271.80(a) to require that, in the case of a donor 1 month of age or younger, you must test a specimen from the birth mother instead of from the donor. We note that requiring testing of the mother is consistent with the standards of several professional organizations (see, e.g., American Association of Blood Banks (AABB) Standards for Hematopoietic Progenitor Cell and Cellular Product Services, 3rd edition, 2002; NMDP Standards, 17th edition, Sept. 1999; Foundation for the Accreditation of Cellular Therapy (FACT)/Netcord International Standards for Cord Blood, 2002; FACT Standards for Hematopoietic Progenitor Cell Collection, Processing and Transplantation, 2nd edition, 2002). Because it is generally accepted that, in most cases, until a month of age the same IgG antibodies are present in the mother's blood as in the neonate's, we decline to add the requested validation requirement.

b. *Timing of specimen collection.* Proposed § 1271.80(b) would require collection of the donor specimen at the time of recovery of cells or tissue from the donor or within 48 hours after recovery, although proposed § 1271.80(b)(1) through (b)(3) would allow specimen collection from a living donor up to 7 days before recovery in certain situations.

We received many comments on this provision.

(Comment 52) One comment recommended that time constraints for specimen storage before testing be consistent with test kit instructions.

(Response) We agree. Section 1271.80(c) requires that you follow the manufacturer's instructions in

performing testing. This includes instructions with respect to storage time before testing.

(Comment 53) Numerous comments asserted that the proposed rule was too restrictive and requested that we allow more time between collection of the specimen and recovery of the cells or tissue. Comments concerned with the recovery of peripheral blood stem/progenitor cells, where recipient conditioning is performed, suggested a timeframe of 30 days before recovery of the HCT/P. Other comments requested that, for cord blood donors, specimen collection be permitted at any time following the donation; another comment requested 7 days. One comment requested from 30 to 90 days post-donation for specimen collection from a sperm donor, citing expense and natural fluctuations in semen sample parameters. Another comment asserted that the proposed time limits were too restrictive for oocyte donors. Some comments expressed concern that, in the case of cadaveric donors, the regulations would not allow testing of specimens collected before death (premortem specimens). Other comments asserted that the requirements on timing of specimen collection would prohibit the use of pretransfusion samples.

(Response) We agree that more time should be allowed between collection of specimens for testing and HCT/P recovery. The final rule requires a sample at the time of recovery, when feasible. However, if specimen collection at the time of cell or tissue recovery is not feasible, you may collect the specimen up to 7 days before or after recovery. We decline to rely on testing for communicable diseases performed later than 7 days before donation, because the test results would not accurately reflect the donor's actual disease exposure at the time of donation. Moreover, as the time period between donation and specimen collection increases, the chances of mix-ups or difficulties with followup also increase. An establishment may choose to perform testing before initiating preparatory regimens on the donor (e.g., oocyte donors require hormone stimulation), but that earlier testing would not replace the testing required by this regulation.

However, we are making an exception for testing donors of peripheral blood stem/progenitor cells. Since the recipient undergoes a myeloablative treatment regiment, i.e., high dose chemotherapy and total body irradiation, it is important to determine the eligibility of the donor before the recipient's treatments begin. At 7 days prior to recovery, the treatment of the recipient has already started and the decision to proceed is irreversible. Therefore, under § 1271.80(b), for donors of peripheral blood stem/progenitor cells only, the establishment may collect the donor specimen up to 30 days before recovery of the stem/progenitor cells. We understand that the current practice of peripheral blood stem/progenitor cell establishments is to take a donor specimen on the day of recovery for additional testing, and we encourage these establishments to continue this practice, in order to permit appropriate followup and treatment if test results are positive.

In response to the comment on semen donation, we have added an exception to § 1271.85(d) that will provide flexibility for the testing of anonymous, repeat semen donors. We understand that, under current practices, establishments do not collect a specimen for testing at each donation by a repeat semen donor. As long as a specimen has been taken and tested, and the donated semen is quarantined pending the results of retesting at least 6 months after donation, it is not necessary for us to restrict this practice through these regulations. For this reason, we have added an exception to § 1271.85(d) for repeat semen donors from whom a specimen has already been collected and tested, and for whom retesting is required under § 1271.85(d). We reiterate that you must collect a new specimen and test it under § 1271.85(d) at least 6 months after the donation, and pending the completion of that retesting you must quarantine the donated semen under § 1271.60(a).

Under the new regulatory language in § 1271.80(b), which permits the collection of a specimen up to 7 days before recovery of cells or tissue, you may use a premortem specimen to test a cadaveric donor, as long as the specimen is collected within that timeframe. The use of specimens taken pretransfusion or preinfusion will continue to be allowed, subject to the same 7-day timeframe; use of these specimens is discussed in section III.C.8.g of this document.

c. *Approved tests.* Proposed § 1271.80(c) would require the use of appropriate FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions (except that, for *Chlamydia trachomatis* and *Neisseria gonorrhea*, tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population must be used until screening tests are available). In addition, proposed § 1271.80(c) would require the use of tests specifically labeled for cadaveric specimens, when applicable and available, instead of more generally labeled donor screening tests.

(Comment 54) Two comments suggested that § 1271.80(c) describe the circumstances in which tissue establishments may use tests that are not licensed, cleared, or approved.

(Response) We decline to make this change. This section requires the use of FDA licensed, approved, or cleared screening tests. The use of unapproved tests would not meet the requirements of this regulation.

(Comment 55) One comment urged FDA to work with laboratories and manufacturers of diagnostic tests to approve tests for cadaveric specimens. Other comments noted that there were no FDA-licensed screening kits for cadaveric blood samples. Another comment expressed doubts that cadaveric blood tests for corneas would be approved.

(Response) FDA has encouraged manufacturers of in vitro diagnostic products to develop products intended for use with cadaveric specimens. Since the publication of the proposed rule, we have licensed test kits specifically labeled for use with cadaveric blood specimens. These test kits must be used, if applicable, when testing all cadaveric HCT/P donors, including cornea donors. A list of licensed test kits for use with cadaveric specimens may be found at *http://www.fda.gov/cber/products/testkits.htm.*

d. *CLIA certification.* Proposed § 1271.80(c) stated, in part, that testing must be performed by a laboratory certified to perform testing on human specimens under the CLIA.

(Comment 56) Two comments asserted that we should permit testing by laboratories that are exempt from CLIA certification.

(Response) We agree with the comment that not all laboratories that comply with CLIA are certified under CLIA. We have revised § 1271.80(c) to require that required testing must be performed by a laboratory that either is certified to perform such testing on human specimens under CLIA and 42 CFR part 493, or has met equivalent requirements as determined by the CMS. Examples of the latter are Veterans Administration hospital laboratories, laboratories in states that have received an exemption from CMS, and laboratories accredited by certain approved accrediting organizations.

(Comment 57) Comments also urged us to permit testing by foreign laboratories subject to requirements equivalent to or more stringent than those imposed by CLIA. One comment

requested that we consider allowing U.S. citizens access to cord blood units from foreign tissue banks, which would not follow CLIA standards but would have similarly regulated clinical laboratory testing.

(Response) We decline to make the change requested because it is not feasible for us to identify and assess the equivalence of other countries' requirements, keep track of any changes to those requirements, and then to ascertain that each foreign tissue bank meets those requirements. In contrast, CLIA certification provides a uniform, workable mechanism for determining laboratory proficiency. Foreign establishments are not prohibited from using domestic CLIA-certified laboratories for performing the required testing, and some firms operating under part 1270 send samples ahead to the United States for testing in CLIA-certified laboratories.

When we first issued regulations on human tissue, one major concern was the distribution in the United States of imported tissue from donors who had not been adequately screened and tested to prevent the transmission of infectious disease (62 FR 40429 at 40435, July 29, 1997). The proficiency of the laboratory performing the required testing is a key element in assuring the safety of HCT/Ps. Certification under CLIA helps to ensure that the laboratory is proficient and competent to perform the required tests accurately. Moreover, any laboratory, foreign or domestic, may apply for certification under CLIA. At this time, we are aware of 21 foreign CLIA-certified laboratories.

e. *Ineligible donors.* Proposed § 1271.80(d)(1) stated that a donor whose specimen tests repeatedly reactive or positive must be determined unsuitable.

We have made several changes to the wording of this paragraph. As discussed earlier in this document, "unsuitable" is now "ineligible."

In addition, for consistency with other FDA regulations, we have changed "repeatedly reactive" to "reactive." As noted in the preamble to the proposed rule, repeatedly reactive means initially reactive, and then reactive in at least one of two duplicate tests with the same manufacturer's test kit (64 FR 52696 at 52705). Deleting the word "repeatedly" from the regulation should allow for future advancements in testing, when the process of repeating an initial reactive result in duplicate would no longer be appropriate. This modification does not affect the requirement that you follow the testing protocol set out in the test kit instructions (§ 1271.80(c)). In other words, if the test kit instructions direct you to repeat an initial reactive test result in duplicate, you must do so. In such cases, the term "reactive" should be understood to mean repeatedly reactive.

Proposed § 1271.80(d)(1) contained two exceptions to the general rule that a donor whose specimen tests reactive or positive must be determined ineligible. Under the first exception, a reactive test for CMV would not make a donor unsuitable unless additional testing showed the presence of an active infection. The second exception was for a donor whose specimen tested repeatedly reactive on a nontreponemal screening test for syphilis and negative on a specific treponemal confirmatory test.

(Comment 58) One comment asserted that FDA should permit confirmatory tests to prevail in all cases, arguing that this is consistent with medical practice and would prevent discarding transplantable tissue. Another comment noted that proposed § 1271.80(d)(1) contained no exception for HBV, although tests for HBV recognize the validity of confirmatory testing in the manufacturer's instructions.

(Response) We disagree that the results of confirmatory tests rather than the results of screening tests should determine donor eligibility. Confirmatory tests may not be as sensitive as screening tests in detecting early infection. Our decision is consistent with the agency's policy in blood regulation: For blood donors, supplemental testing is used for donor reentry or for donor notification and counseling.

Confirmatory testing for HBV, such as the hepatitis B surface antigen (HBsAg) neutralization assay, is valuable for confirming the presence of HBsAg in specimens found to be reactive by a screening assay, and so can be helpful for donor counseling. However, the neutralization assay may not always detect all potentially infectious HCT/Ps. Therefore, we are not making an exception in this section that would permit a donor-eligibility determination based on HBV confirmatory testing.

(Comment 59) One comment, submitted to the CGTP docket, asked us to allow tissue banks to use the results of triplicate testing, performed by laboratories for OPOs, when all three tests are negative.

(Response) If you are using test results of an enzyme immunoassay obtained by an OPO, and the test was initially run in triplicate, you may interpret three nonreactive results in a single run as a negative test result.

f. *Testing for CMV.* Proposed § 1271.85(b)(3) would require that donors of viable, leukocyte-rich cells or tissue be tested for CMV. Proposed § 1271.80(d)(1)(i) would require you to determine ineligible a donor whose specimen tests reactive for CMV, unless additional testing does not show the presence of an active infection. We proposed the exception in § 1271.80(d)(1)(i) because, although a donor with active CMV poses a risk of CMV transmission, a donor's past infection with the virus does not necessarily present such a risk (64 FR at 52705). We noted that the results of CMV testing would accompany the HCT/P, and we specifically requested comments on this approach (64 FR 52705).

(Comment 60) One comment noted that the proposed rule did not specify a means for assuring that CMV viral shedding is not occurring, and suggested that we specify the type of tests to use to determine the presence or absence of viral shedding.

(Response) Considering this comment has led us to conclude that it would be difficult to comply with the terms of the exception in proposed § 1271.80(d)(1)(i). Therefore, we have made several modifications to the final rule with respect to CMV testing. The effect of these changes is to require CMV testing of donors of leukocyte-rich cells or tissue, while allowing the use of HCT/Ps from CMV-reactive donors in some instances.

First, we have deleted proposed § 1271.80(d)(1)(i) from the final rule, and we have removed CMV from the list of relevant communicable disease agents and diseases in § 1271.3(r)(1), as well as from § 1271.85(b)(3). We have made this change because we believe that, as proposed, the rule may have led all donors who test reactive for CMV to be disqualified, an undesirable result.

Second, although we have removed CMV from the list of relevant communicable disease agents and diseases in § 1271.3(r)(1), we have not removed the requirement for CMV testing from the final rule altogether. An HCT/P from a CMV-antibody-reactive donor is capable of transmitting CMV to a recipient who tests negative for CMV antibody, and in some recipients this can have serious consequences. To prevent these consequences, the final rule, at § 1271.85(b)(2), requires you to test donors of viable leukocyte-rich cells and tissue for evidence of infection due to CMV. Under § 1271.55(b), results of testing (including testing for CMV) must accompany an HCT/P.

The third change we have made in the final rule is to require, in § 1271.85(b)(2), that you establish and maintain an SOP governing the release

of an HCT/P from a donor whose specimen tests reactive for CMV. This approach will permit the development of procedures that are specific to different situations. SOPs might, for example, permit the release of an HCT/P from a donor with a CMV-antibody reactive test, depending on the CMV status of the recipient. We address the issue of the use of HCT/Ps from CMV-reactive donors in the donor-eligibility draft guidance, announced elsewhere in this **Federal Register**.

(Comment 61) Another comment asked whether a semen bank would be able to use a semen donor who tested positive for CMV (IgG) in a CMV positive (IgG) recipient.

(Response) Section 1271.85(b)(2), in part, requires you to establish and maintain an SOP governing the release of an HCT/P from a donor whose specimen tests reactive for CMV. Thus, your SOP would need to address this situation. We discuss the use of semen from a donor who tests reactive to CMV (IgG) in the donor-eligibility draft guidance announced elsewhere in this **Federal Register**.

(Comment 62) One comment suggested that we used the term "repeatedly positive" instead of "repeatedly reactive" when describing results of CMV testing, because the term "repeatedly reactive" is not recognized as a CMV screening test result.

(Response) As discussed, we have changed the wording from "repeatedly reactive" to "reactive." Although the labeling of the devices used to perform CMV testing describes results as positive or negative, the terms "positive" and "reactive" are synonymous in this context for the purposes of this rule.

(Comment 63) One comment asserted that, for reproductive cells, it is unnecessary to require the CMV status to accompany the product, because approximately 40 percent of semen donors are CMV antibody (IgG) positive. The comment noted that it is rare for the physician conducting the insemination to review this information, and that, for this reason, the information is provided only upon request.

(Response) We disagree. CMV is the most commonly identified cause of congenital infection (Krugman S., et al., Infectious Diseases in Children, St. Louis, CV Mosby, pp. 8–21, 1985). If a CMV negative pregnant woman contracts CMV, the fetus may acquire congenital CMV infection. We continue to believe that information about the semen donor's CMV status should appear in materials accompanying the HCT/P, so that physicians may rely on this information to make informed decisions about the use of an HCT/P in a particular patient's situation.

g. *Plasma dilution.* The transfusion or infusion of blood, colloids, or crystalloids may result in plasma dilution, which can affect the results of communicable disease testing. Section 1271.3(p) defines plasma dilution as a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies.

Proposed § 1271.80(d)(2) and (d)(3) would set out requirements relating to plasma dilution. We have reorganized those provisions in this final rule, and they now appear in paragraph (d)(2).

The final rule requires you to determine ineligible any donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected, unless you: (1) Test a specimen taken before transfusion or infusion (and up to 7 days before recovery of cells or tissue), or (2) analyze the extent of plasma dilution, using an established procedure called an algorithm. If that analysis rules out plasma dilution sufficient to affect test results, then you can perform required testing on a specimen taken after transfusion or infusion. However, if plasma dilution is sufficient to affect results, and no specimen taken before transfusion or infusion is available, then the donor is ineligible to donate.

The final rule gives examples of clinical situations in which you must suspect plasma dilution sufficient to affect test results. Under § 1271.80(d)(2)(ii)(A), if you know of or suspect blood loss in a donor over 12 years of age, transfusions and infusions totaling more than 2,000 milliliters (mL) must be suspected of affecting test results. Under § 2171.80(d)(2)(ii)(B), any transfusion or infusion in a donor 12 years of age or younger must be suspected of affecting test results, whether or not blood loss has occurred. These clinical situations were set out in the proposed regulation and were based closely on § 1270.20(h)(2) and (h)(3).

However, whereas the proposed rule specified the timeframe for these transfusions or infusions as within 48 hours of specimen collection (or within 1 hour in the case of crystalloids), the final rule sets the timeframe as within 48 hours (or one hour, for crystalloids) before death or specimen collection, whichever occurred earlier. We have inserted the reference to death to take into account those situations where the specimen is collected after death. For example, if the specimen is collected 3 days after death, it does not make sense to consider transfusions within the 48 hours before specimen collection, when the donor would already be dead and would not be receiving transfusions. What is relevant in this instance is any transfusion or infusion within 48 hours of the donor's death (or one hour, for crystalloids).

As we noted in the guidance document that accompanied part 1270, every possible clinical situation cannot be predicted, and there may be additional circumstances where plasma dilution sufficient to affect test results should be suspected. As restructured, § 1271.80(d)(2) recognizes that these other situations exist. In the donor-eligibility draft guidance announced elsewhere in this issue of the **Federal Register**, we list additional circumstances in which it may be necessary to employ an algorithm.

A discussion of plasma dilution and algorithms appeared in the final rule "Human Tissue Intended for Transplantation" issued in the **Federal Register** of July 29, 1997 (see 62 FR 40429 at 40435 through 40436), and also in a guidance document entitled "Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation" dated July 1997. We now refer to those documents. We also note that the donor-eligibility draft guidance announced elsewhere in this issue of the **Federal Register** contains information on appropriate algorithms.

(Comment 64) One comment requested clarification of the term "blood loss."

(Response) By blood loss, we mean bleeding, including internal bleeding. Thus, in considering whether blood loss has occurred in a potential donor, you should consider both blood lost within the body cavity and blood lost outside of the body.

(Comment 65) One comment questioned how to determine whether to use an algorithm due to the 2000 mL limit without actually performing the tabulation.

(Response) You may need to review medical records to make a rough determination of the total amount of blood, colloids, or crystalloids administered to a potential donor. This threshold determination will allow you to decide whether further analysis, using an algorithm, is necessary. In an adult with blood loss, if the total exceeds 2,000 mL, and administration took place within the timeframes set out in § 1271.80(d), then you must suspect plasma dilution sufficient to affect test results. Section 1271.80(d)(2) would then require you either to test a specimen taken before infusion or transfusion or to use an appropriate algorithm to analyze further the possibility of plasma dilution.

(Comment 66) One comment asserted that including the total volume of whole blood in calculations does not meet scientific principles, because the volume of the red blood cells does not contribute to plasma dilution.

(Response) The calculations that are made to determine if plasma dilution has occurred depend upon the category of fluids transfused or infused. The three categories are blood (e.g., whole blood, red blood cells); colloids (e.g., dextran, plasma, platelets, albumin, hetastarch); and crystalloids (e.g., saline, dextrose in water, Ringer's lactate). If the donor has received colloids in the 48 hours before death or specimen collection, and/or crystalloids in the one hour before death or specimen collection, then a comparison of the total volume of these fluids with the donor's plasma volume would be sufficient to determine if plasma dilution has occurred. However, when the fluids transfused are in the "blood" category (alone, or in combination with colloids and/or crystalloids), a comparison of the total volume of these fluids with the donor's blood volume should be performed, in addition to a comparison of the total volume of colloids and/or crystalloids with the donor's plasma volume.

In the situation described in the comment, a comparison of the estimated volume of plasma contained in whole blood with the donor's plasma volume only (without a comparison of the volume of whole blood with the donor's blood volume) would underestimate the amount of plasma dilution. Thus, a donor might be inappropriately determined to be eligible even though plasma dilution sufficient to affect viral marker testing had occurred.

The draft guidance that accompanies this final rule explains which calculations should be performed for each category of fluids transfused or infused.

The proposed rule referred to "reconstituted blood" under the category of fluids called "blood." We have removed the reference to "reconstituted blood," because we believe it is unnecessary and could lead to confusion in performing the necessary calculations (e.g., in which one of the three categories should reconstituted blood be included?). You should consider reconstituted blood to be whole blood for the purpose of § 1271.80(d)(2), and you should include whole blood in the category of "blood" transfused in the 48 hours before death or specimen collection.

10. What Testing Is Required for Different Types of Cells and Tissues? (§ 1271.85)

Proposed § 1271.85(a) would require you to test donors of all types of cells and tissues for relevant communicable disease agents including, at a minimum, HIV, HBV, HCV, and *Treponema pallidum*. Proposed § 1271.85(b) would apply to viable, leukocyte-rich cells and tissue and would require testing for relevant cell-associated communicable diseases including, at a minimum, HTLV and CMV. Proposed § 1271.85(c) would apply to donors of reproductive cells and tissues and would require testing for relevant genitourinary disease agents, including, at a minimum, *Chlamydia trachomatis* and *Neisseria gonorrhea*. Proposed § 1271.85(d) would require retesting for semen donors. Proposed § 1271.85(e) would require an assessment to detect evidence of TSE for donors of dura mater.

Under the proposed rule, cells or tissues could be subject to more than one testing requirement. For example, you would test a donor of leukocyte-rich reproductive tissue (e.g., semen) for the diseases listed in proposed § 1271.85 (a), (b), and (c).

The preamble to the proposed rule listed the tests that, according to our current thinking, are appropriate to use to test for the disease agents and diseases listed in § 1271.85 (64 FR 52696 at 52705 and 52706). Those testing recommendations are now contained in the donor-eligibility draft guidance.

We have deleted the phrase "at a minimum" from § 1271.85(a), (b), and (c), because it might give the impression that testing is required only for those communicable diseases listed in § 1271.85. Although at this time we only require testing for these diseases, in the future additional diseases may be identified as relevant. As discussed in comment 16 of this document, we will issue guidance that notifies you when we believe additional relevant communicable diseases meet the definition in § 1271.3(r)(2).

a. *Viable and nonviable cells and tissue (§ 1271.85(a))*. Proposed § 1271.85(a) would require donors of all types of cells and tissues to be tested for HIV type 1, HIV type 2, HBV, HCV, and *Treponema pallidum*.

(Comment 67) One comment noted that FDA did not require use of the HIV p24 antigen test for HIV screening. The comment described the test as easily accessible and inexpensive.

(Response) We recommend the particular tests to assess HIV infection in the donor-eligibility draft guidance, and discuss the HIV p24 antigen test.

(Comment 68) One comment discussed the use of core antibody and hepatitis B surface antibody tests to clarify donor HBV infectivity when the donor is HBsAg negative and core antibody positive. The comment asserted that if the IgM core antibody test is negative, and the surface antibody test is positive, this indicates that the donor had a past HBV infection that has resolved. The comment also asserted that the core antibody (IgG) is not a screening test for HBV infectivity, but is a historical test indicating previous infection with HBV.

(Response) Although we agree that, in most cases, a negative IgM core antibody test with a reactive surface antibody test indicates a past infection, we disagree that this combination of results always indicates that the infection has resolved. Rather, this combination of results does not indicate whether the donor is infectious.

In the donor-eligibility draft guidance that accompanies this final rule, we recommend that you use the total core antibody (IgG and IgM) test to test for HBV in addition to the HBsAg test.

(Comment 69) One comment noted that the standard screening test for HCV in Europe is different from the test FDA listed in the preamble to the proposed rule.

(Response) This comment referred to the use of NAT, which has not yet been licensed in this country for the purpose of screening cadaveric tissue donors. FDA encourages manufacturers of NAT kits licensed for blood donor screening to validate NAT for use with cadaveric blood specimens, and to submit the data to FDA to obtain a labeling change, to include this intended use. (Recommended tests are listed in the donor-eligibility draft guidance.)

(Comment 70) We received several comments on the requirement for syphilis testing (*Treponema pallidum*). One comment requested that, if the agency eliminates syphilis testing for blood donors, it should consider eliminating the requirement for tissue donors. Several comments opposed requiring syphilis testing for cornea donors, asserting that transmission is unlikely or that there is no significant health risk to the corneal transplant recipient. One comment supported the requirement for cornea donors.

(Response) We disagree that syphilis testing should not be required for cell and tissue donors, including cornea donors, and note that we have not eliminated syphilis testing of blood donors. In the final rule on testing of blood donors, we noted that comments

did not provide sufficient supporting data to justify eliminating the requirements to test blood and blood components with a serological test for syphilis. Moreover, preliminary results from ongoing studies indicate that the infectivity of seroreactive donors remains the subject of scientific debate. For this reason, we maintained the syphilis testing requirement for blood donors (Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents, Final rule (66 FR 31146, June 11, 2001)).

One comment cited a scientific paper, which we have reviewed (Macsai MS, Norris SJ, "OptiSol Corneal Storage Medium and Transmission of *Treponema pallidum*," *Cornea*, vol. 14(6), pp. 595–600, November 1995). The paper reports the results of a rabbit study on the effects of storage media on the probability of syphilis transmission. Although the media prevented the transmission of syphilis by contaminated corneas, transmission occurred when the media was not used. This paper does not support the lack of syphilis transmissibility by corneas; indeed, it shows the opposite. For this reason, we do not believe this study provides sufficient evidence to support eliminating the proposed syphilis testing requirement. Moreover, we disagree with the comment's assertion that there is no significant health risk to the corneal transplant recipient. Although treatable, syphilis remains a serious disease.

b. *Leukocyte-rich cells and tissues (§ 1271.85(b))*. Proposed § 1271.85(b) would require testing for HTLV, type I; HTLV, type II; and Cytomegalovirus for donors of viable, leukocyte-rich cells and tissue.

(Comment 71) We received several comments on our proposal to distinguish between leukocyte-rich cells and tissue and other cells and tissue, and on our preamble discussion of which cells and tissues we consider leukocyte-rich (64 FR 52696 at 52705). One comment noted that the differentiation was helpful. The comment suggested adding cultures of certain cell types, such as fibroblasts, to the list of materials that are not considered to be leukocyte-rich. Two comments asserted that oocytes and embryos are not leukocyte-rich. One comment noted that the term "stem cells," listed in the preamble as an example of leukocyte-rich cells or tissue, is too broad, and would apply to corneal epithelial stem cells, which are not leukocyte-rich. Another comment agreed that semen can be characterized as leukocyte-rich tissue but asserted that treated or "washed" sperm do not pose the same disease risks.

(Response) We agree with the comment requesting a more precise description of those stem cells that are rich in leukocytes, and we will refer to those cells as hematopoietic stem/progenitor cells. We also agree with the comments asserting that oocytes and embryos are not leukocyte-rich.

However, we disagree that sperm that has been treated or washed should be treated differently, for the purposes of these testing requirements, from semen. The HCT/P initially donated is semen, which is leukocyte-rich; thus, the donor must be tested for HTLV–I and –II and CMV. The donated semen poses risks; for example, it could transmit communicable disease to those handling it, or it could be released improperly before further processing. Later processing may decrease or remove the leukocytes from the donated semen, but would not affect the testing that must be performed on the donor at the time of donation. These testing requirements apply at the time of donation, regardless of how the HCT/P might later be processed.

For the same reason, we decline to state whether or not cultures of certain cell types, such as fibroblasts, are rich in leukocytes. As with semen, the HCT/P initially donated is not the fibroblast, but some other tissue from which fibroblasts are isolated. Thus, the applicable testing requirements depend on whether or not the donated cells or tissue are leukocyte-rich.

(Comment 72) One comment asserted that HTLV–I/II and CMV testing is not relevant to corneal transplants.

(Response) We agree. As noted in the preamble to the proposed rule (64 FR 52696 at 52705), corneas are not rich in leukocytes, so § 1271.85(b) does not apply to them. The donor-eligibility draft guidance contains our current thinking about which cells and tissues are leukocyte-rich.

(Comment 73) One comment asked how to counsel donors of reproductive tissue who test positive for HTLV. Another comment noted that diagnosis of some infections, such as HTLV, would lead to serious consequences for those individuals who test positive.

(Response) We recognize that it may be difficult to counsel patients about the results of HTLV testing; however, the scope of this rule does not extend to issues of donor notification.

(Comment 74) One comment asserted that, because leukocyte-rich, nonviable lymphocytes may transmit latent HTLV and CMV, they should be tested.

(Response) We agree that these lymphocytes must be tested. However, we do not consider them to be nonviable. Although they do not proliferate, they are live cells, which means cells that have the ability to metabolize or divide, and thus "are viable."

(Comment 75) One comment asserted that CMV testing is not necessary for oocyte donors because the virus does not appear to infect oocytes or surrounding cells.

(Response) We agree that CMV testing is not necessary for oocyte donors. Oocytes and embryos are not considered leukocyte-rich.

c. *Reproductive cells and tissues (§ 1271.85(c))*. Proposed § 1271.85(c) would list relevant communicable disease agents and diseases of the genitourinary tract for which you would test a donor of reproductive cells or tissue. The proposal would exclude reproductive cells or tissues procured 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.

(Comment 76) One comment asserted that most oocytes are retrieved through vaginal ultrasound techniques, so the exception to testing for chlamydia and gonorrhea would not apply in most cases.

(Response) We agree with this comment that, in most instances, oocytes are removed transvaginally, and so the exception in § 1271.85(c) would not apply; thus, testing would be required. However, if you use vaginal ultrasound for visualization only, and retrieve the oocytes in a way that ensures freedom from contamination with infectious disease organisms (e.g., nonvaginal laparoscopy), then the exception would apply.

d. *Retesting (§ 1271.85(d))*. Proposed § 1271.85(d) would require retesting of donors of "reproductive cells or tissue that can be reliably stored."

We have rewritten this provision to apply only to anonymous donors of semen. We discuss the reasons for this change elsewhere in this final rule in comment 35 of this document.

(Comment 77) Several comments expressed concern that retesting would be required for all tissues that can be reliably stored, not simply reproductive cells and tissue.

(Response) This was not our intention. As noted previously, § 1271.85(d) requires retesting only for semen from anonymous donors.

(Comment 78) The preamble to the proposal recommended that, where appropriate and feasible, all living donors of banked tissue be retested 6 months after donation (64 FR 52696 at 52706). Several comments objected to

the recommendation and asserted that retesting donors of nonreproductive cells and tissue would be onerous, costly, and inefficient.

(Response) At the time of initial testing, a donor may test negative but still be in the infectious window period. For this reason, retesting living donors of banked tissue 6 months after donation is an added safeguard for the prevention and spread of communicable diseases. However, in response to the comments, we are not adopting this requirement in this final rule.

e. *Dura mater (§ 1271.85(e))*. Proposed § 1271.85(e) would require, for donors of dura mater, an assessment designed to detect evidence of TSE. The preamble to the proposed rule described procedures for complying with the assessment requirement (see 64 FR 52696 at 52706). These procedures included, after removal of the dura mater, a full brain autopsy of the donor, including gross and histological examination, performed by a qualified neuropathologist, to identify evidence of TSE changes. The preamble also noted that, although there is no FDA-approved or validated test for screening TSE in brain tissue, a negative test to detect protease-resistant prion protein (PrP-RES), either by immunohistochemistry or Western Blot, is considered significant in increasing the level of confidence that the brain and the dura mater are free of TSE.

(Comment 79) Several comments supported the proposed requirement and the procedures set out in the preamble. One comment noted that the precautions of a full brain autopsy in addition to donor screening and medical history are a necessary step until there is an approved screening test. One comment asserted that a brain autopsy for dura donors is not feasible and recommended a brain biopsy instead. Two comments suggested that we change our recommendation that the autopsy be performed by a qualified neuropathologist to a qualified pathologist.

(Response) We based the recommendations in the preamble to the proposed rule on conclusions reached by FDA's TSEAC at meetings held on October 6, 1997, and April 16, 1998. The committee reiterated these recommendations at a meeting on January 18, 2001. The committee recommended a full brain autopsy of the donor, including gross and histological examination, to identify evidence of TSE changes. We agree with comments that a brain autopsy is necessary in the absence of an appropriate test, and will consider changing the requirement in the future if a sufficiently sensitive test is approved. A brain biopsy, although less expensive and intrusive, may not provide adequate information on TSE changes, because these changes may occur focally in the brain. Moreover, it has not been validated as a predictor of TSE. For these reasons, we decline to change that aspect of our recommendation.

However, we have reconsidered our proposal that the assessment be performed by a qualified neuropathologist. We recognize that many institutions do not have a neuropathologist on staff, and that many pathologists are qualified to do this assessment. For this reason, we now recommend that a qualified pathologist perform the assessment. To be qualified, the pathologist needs to have the appropriate training or experience to perform the appropriate neuropathologic examination.

We have modified the regulation slightly to require that the assessment performed on donors of dura mater be "adequate." The previous discussion provides our current understanding of what would constitute an adequate assessment.

(Comment 80) The preamble to the proposed rule noted that the type of TSE testing required for donors of dura mater did not appear feasible for cornea donors, and we requested comments on this issue (64 FR 52696 at 52706).

Several comments agreed that TSE testing for corneal tissue donors is not a feasible option because of the time required for brain autopsy or biopsy. The comments also cited concerns about costs and a potential decrease in donation rates. One comment noted that the use of all available screening components, including the medical screening interview, would satisfactorily substitute for TSE testing.

(Response) Under present conditions of storage in the United States, corneas must be transplanted within days of procurement to maintain their utility. For this reason, it is not feasible to test cornea donors for TSE using current methodologies, and we are not imposing a testing requirement at this time. However, under § 1271.75(a), screening for TSE is required for donors of all types of tissues.

11. Are There Exceptions From the Requirement of Determining Donor Eligibility, and What Labeling Requirements Apply? (§ 1271.90)

Proposed § 1271.90 would recommend, but not require, screening and testing for banked cells and tissues for autologous use and reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use. Proposed § 1271.90 would require special labeling for these HCT/Ps. We have added appropriate warning label requirements to § 1271.90.

(Comment 81) Several comments supported our proposal to recommend that the requirements for infectious disease testing be applied to HCT/Ps designated for autologous use. Two comments expressed concern that the recommendations in proposed § 1271.90(a) pertaining to reproductive tissue would have the same effect as requirements.

We recognize that a codified recommendation may carry more force than we intended. For this reason, although we recognize that many establishments will screen and test donors of autologous and reproductive HCT/Ps that fall within the exceptions in § 1271.90, and we believe there are valid reasons for doing so, we have deleted the recommendation from the codified section.

(Comment 82) One comment pointed out that the rules of safe laboratory operation dictate that laboratory personnel be informed of the risks in handling autologous donations. Another comment requested that we add to § 1271.90(b) the requirement that these HCT/Ps be handled as untested in accordance with § 1271.60.

Although we agree with the concerns expressed in the comments, we decline to amend § 1271.90(b) as suggested by the comments. The labeling required in § 1271.90(b) (e.g., "NOT EVALUATED FOR INFECTIOUS SUBSTANCES") should alert personnel to the risks of these HCT/Ps.

(Comment 83) One comment questioned whether proposed § 1271.90(a)(2) referred to semen, ova, and embryos.

(Response) Semen, ova, and embryos are examples of reproductive cells and tissues included in § 1271.90(a)(2).

(Comment 84) Two comments questioned how § 1271.90 would apply to individual semen donors who wish to cryopreserve their semen (e.g., cancer patients).

(Response) If the semen donor intends that the cryopreserved sperm be used with a sexually intimate partner, then § 1271.90 applies.

After reviewing these comments, we also realized that cryopreserved reproductive cells or tissue for autologous use or for use by a sexually intimate partner, originally exempted from the donor screening and testing requirements, could be subsequently used for directed donation. Therefore, we have added an exception to the rule to accommodate individuals whose reproductive options have been restricted due to health or infertility.

These individuals may not have undergone testing at the time of donation, because their intention at that time was autologous use or use in a sexually intimate partner. For various reasons, the donor(s) cannot make additional donations (e.g., the woman is post-menopausal or has her ovaries and uterus removed; the man has undergone chemotherapy, which renders him infertile.) To permit use of such cryopreserved cells or tissue for directed donation in situations where subsequent screening and testing is available, we have added § 1271.90(a)(3).

Section 1271.90(a)(3) states that cryopreserved cells or tissue for reproductive use, which were originally intended for autologous use, or use in a sexually intimate partner (and therefore the donor(s) were not tested at the time of donation) may subsequently be used for directed donation, provided that a donor cannot make additional donations of HCT/Ps due to infertility, or health; and appropriate measures are taken to screen and test the donor(s) before transfer to the recipient. The agency intends to address, in guidance, the appropriate methods for screening and testing donors in such circumstances to determine whether the HCT/Ps may carry communicable diseases.

An example is the situation in which a sexually intimate couple create embryos, some of which are cryopreserved. The donors were not screened and tested at the time of the donation. The woman subsequently has her ovaries and uterus surgically removed, due to cancer. The donor couple wishes to make a directed donation of the cryopreserved embryos to a recipient who is known to one or both of the donors prior to the donation. Under § 1271.90(a)(3), the embryos would be eligible for directed donation provided the couple can now be screened and tested.

(Comment 85) One comment opposed the exception in proposed § 1271.90 for sexually intimate reproductive tissue donors. The comment asserted that all reproductive tissue donors should be screened, because sexually intimate partners may have escaped exposure to each other's bodily fluids.

(Response) Although we agree that screening and testing may be appropriate for sexually intimate partners, and encourage establishments to perform screening and testing, we believe that this should be the responsibility of the attending physician, the donor, and the recipient.

E. Economic Impacts

(Comment 86) Five comments suggested that we significantly underestimated the rule's economic impact and that significant changes in the SOPs of all eye banks would be required.

(Response) We do not agree. Current industry standards meet or exceed most of the specifications of this final rule and industry consultants have indicated that compliance with these standards is nearly 100 percent. Based on this information, we do not believe that SOPs will need to be substantively changed as a result of this final rule. Furthermore, these comments did not provide any data that refute or would cause us to adjust our estimates of the economic impacts.

(Comment 87) One comment suggested that cost increases are not easily absorbed by the not-for-profit eye banking community, and that a rule could negatively affect the availability of and/or access to services.

(Response) We do not agree. Many similarities exist between the provisions of this final rule and current industry standards. Furthermore, our Analysis of Economic Impacts suggests only a minor compliance cost burden, which will not significantly affect the availability of and/or access to services.

(Comment 88) One comment suggested that user fees could potentially add to the rule's economic impact.

(Response) A user fee is not a component of this final rule.

(Comment 89) Two comments stated that the rule will impose compliance costs of $10,000 to $20,000 per average tissue and eye bank, and that the effects of the regulation on hospitals may push this figure higher.

We do not agree with these estimates of compliance costs. Furthermore, we are not able to address their validity as no information or data were provided to support them. We are also unable to address the rule's effects on hospitals as alluded to by the comments, because the comments did not provide any data that would allow us to evaluate the alleged effects.

(Comment 90) One comment objected to our $1.23 million estimate of average annual eye bank establishment income and noted that "* * * many U.S. eye banks operate within budgets that are <50% of that figure."

(Response) We realize that these figures may vary. Our average annual income estimate was intended to provide insight as to the financial burden of this rule for a representative establishment. Some establishments would be expected to have income greater than $1.23 million and others less than $1.23 million. While we recognize that the financial impact of regulations on small business entities is an important consideration under The Regulatory Flexibility Act, our analysis suggests this final rule will not have a significant economic impact.

(Comment 91) One comment objected to our estimate of the cost of testing tissue donors for syphilis, suggesting that such testing will cost $15 per donor and that testing 650 donors will increase costs by approximately $10,000.

(Response) We do not dispute these figures. However, there is no indication given in the comment as to whether this is a significant cost impact, and/or for which types of establishments (i.e., small versus large). These figures are accurate, but would be of greater value if presented in context, e.g., as a percentage of establishment revenues.

(Comment 92) One comment noted that there was no discussion of the costs of the forthcoming "good manufacturing practices" rule.

(Response) We believe the comment is referring to the compliance costs associated with the forthcoming CGTP rules, which are not a part of this final rule. We will include a full economic analysis of the forthcoming CGTPs when that final rule is published.

(Comment 93) Four comments objected to a quarantine requirement for donated oocytes and embryos. These comments suggested that this requirement is unnecessary and unacceptable due to the excessive burden placed on reproductive clinics, physicians, and patients.

(Response) The 6-month quarantine requirement for reproductive tissues now applies only to semen from anonymous donors, and not to oocytes or embryos.

(Comment 94) One comment suggested that testing and screening of oocyte and embryo donors would need to be repeated after a 6-month quarantine, resulting in additional costs.

(Response) This final rule does not require retesting of oocyte and embryo donors. Therefore, there is no need to include these costs in the economic analysis.

(Comment 95) One comment suggested that the private sector would have to spend more than $100 million per year to comply with this final rule, requiring a cost-benefit analysis.

(Response) We do not agree. Based on our analysis, the costs of complying with this final rule are far less than $100 million per year, and therefore a cost-benefit analysis is not required. Furthermore, no data were provided in the comment to support its estimate of compliance costs.

(Comment 96) Three comments objected to our estimate of the cost of

screening and testing oocyte donors and suggested that the actual cost is much higher.

(Response) We agree that this cost may be higher, and have revised our Analysis of Economic Impacts to reflect the most recent cost data available.

(Comment 97) One comment suggested that our estimate of the cost of a donor oocyte cycle is too low.

(Response) We realize that these figures may vary. However, comments from another ART facility indicate that our cost estimate for a donor oocyte cycle (originally obtained from a study published in the journal Fertility and Sterility) is reasonable (Ref. 26).

(Comment 98) One comment suggested that our estimate of the average revenue of ART centers was too high.

(Response) We do not agree. The comment assumes the cost of an IVF cycle is $10,000, whereas we assume the average cost of an ART cycle is $11,868, a more general and somewhat larger number. Furthermore, the comment presents a net average revenue estimate for ART facilities, after subtracting drug costs and oocyte retrieval fees. In the proposed rule, we present a gross average revenue estimate. It is therefore unclear that these estimates of average revenue can be meaningfully compared.

IV. Analysis of Economic Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (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 Unfunded Mandates Reform Act requires that agencies prepare a written statement under section 202(a) of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) in any one year. The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant economic impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact.

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action as defined by the Executive order, and so, is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. As explained in section IV.C of this document, the agency believes that most facilities would not be significantly affected by this final rule because they are already performing the infectious disease screening and testing and recordkeeping that is being required. However, FDA does not have sufficient data to fully characterize the size distribution and other relevant features of small entities, particularly those involved with reproductive HCT/Ps, and the impact on these entities is uncertain. The following analysis, along with this preamble, represents FDA's Final Regulatory Flexibility Analysis.

Based on the following economic analysis, FDA estimates that the total one-time costs to comply with this final rule will be between $0.4 and $2.1 million, and the annual or recurring costs will be between $1.8 and $3.5 million. These figures imply a total annualized cost estimate of between $1.9 and $3.8 million. The average annualized cost per affected entity, expressed as a percentage of average annual revenue, ranges from 0.003 to 0.35 percent. FDA has provided ranges of cost estimates to account for uncertainty with respect to both the number of entities affected, and the degree to which affected entities are already performing the activities required by this final rule.

A. Objectives and Basis of the Proposed Action

FDA is publishing this final rule as the next step in establishing regulations for the rapidly evolving HCT/P industry. This final rule is needed to prevent unwitting use of contaminated tissues with the potential for transmitting infectious diseases, including HIV and hepatitis.

While acting to increase the safety of the nation's supply of HCT/Ps, FDA is implementing regulations in a way that will avoid unnecessary requirements. To minimize burdens while maintaining safety, the agency has designed the screening and testing provisions to vary with the specific type and use of each HCT/P. This regulatory action is focused on the prevention of disease transmission through implantation, transplantation, infusion, or transfer of any HCT/P. For example, FDA will now require cell and tissue donors to be tested for syphilis and screened for TSE. Donors of viable, leukocyte-rich cells or tissue will also be tested for HTLV types I and II, and CMV. Because communicable disease agents can be transmitted by semen and other genitourinary secretions, FDA is requiring that certain donors of reproductive cells and tissue be screened and tested for sexually transmitted diseases. FDA is also amending the existing CGMP regulations for drugs and QS regulations for medical devices to clarify the scope of the screening and testing requirements in part 1271, subpart C.

FDA's objectives and authority for issuing this final rule are described in detail in section II of this document. FDA is relying on the authority provided by section 361 of the PHS Act to issue regulations to prevent the spread of communicable disease, as well as its authority under the act to issue CGMP regulations for drugs (21 U.S.C. 351(a)(2)(B)). FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with this final rule.

This final rule provides oversight for the full spectrum of HCT/Ps that are now marketed and may be marketed in the future. This action will improve protection of the public health and increase public confidence in new technologies, while imposing a minimal regulatory burden. An important benefit of this final rule is that it will establish a consistent standard of safety for marginal firms not currently following voluntary industry standards and guidelines and help to ensure equivalent protection from transmissible diseases for all recipients of therapy involving HCT/Ps, regardless of the health condition for which they are being treated. This final rule will help minimize the risk to all HCT/P recipients of exposure to several life-threatening, in some cases incurable, diseases, including HIV, HBV, HCV, CJD, HTLV, CMV, and others. These risks will be minimized through validated screening procedures, lab tests, recordkeeping and adequate product labeling to avoid unwitting use of unsafe HCT/Ps.

B. The Type and Number of Entities Affected

This final rule requires manufacturers of HCT/Ps to screen and test the donors of cells and tissue used in those products. The rule requires that donors be screened and tested for risk factors for, and clinical evidence of, a relevant communicable disease agents and diseases. This final rule applies to a range of activities conducted at facilities such as conventional tissue banks, eye banks, semen banks, infertility treatment centers, and facilities processing hematopoietic stem/progenitor cells.

Information obtained under the registration final rule forms the basis for FDA's estimates of the number of affected eye banks and conventional tissue banks. The agency has not yet received all registration and listing information from reproductive tissue and hematopoietic stem/progenitor cells establishments, because registration and listing requirements for such establishments and products have not yet gone into effect. The agency's estimates of the number of affected eye banks, hematopoietic stem/progenitor cell facilities, semen banks and ART facilities rely heavily on information obtained from various professional organizations associated with the HCT/P industry. Where good statistical data are not available, FDA's estimates have incorporated the quantitative judgments of individual experts identified through contacts with HCT/P industry professional associations.

As presented in table 1 of this document, FDA has a record of 134 registered facilities listing eye tissue including 96 eye banks, 93 of which are currently accredited by EBAA. FDA also has a record of 166 registered tissue banks involved in the manufacture of other conventional HCT/Ps, e.g., pericardium, dura mater, heart valves, skin and bone allografts, fascia, tendons and ligaments (hereafter referred to as "conventional tissue banks"). The American Association of Tissue Banks (AATB) lists approximately 75 accredited tissue banks and projects an additional 40 to 60 members not accredited.

Facilities that produce hematopoietic stem/progenitor cell products from peripheral blood or umbilical cord blood will also be affected by this final rule. FDA finds that available data with which to estimate the number of peripheral blood stem/progenitor cell (PBSC) facilities and evaluate current practices are quite limited, and the actual number of PBSC facilities may range from 200 to 400. As of April 2002, CBER has a record of 178 voluntarily registered facilities listing "stem cell" as a type of product or establishment. The National Marrow Donor Program (NMDP), which includes establishments that recover PBSCs, lists approximately 92 donor centers and 113 collection centers. Approximately 150 facilities involved with PBSC production are currently accredited by AABB and an estimated 107 are accredited by the Foundation FACT. Industry sources estimate that approximately 80 of these facilities have or are seeking dual AABB/FACT accreditation, suggesting an unduplicated count of approximately 200 PBSC facilities assumed to be accredited by the AABB and/or FACT. However, the number and donor screening and testing practices of nonaccredited facilities are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of blood or bone marrow facilities may be as high as 400 (e.g., 200 more than the number estimated to be accredited by AABB and/or FACT), but the number of IBMTR/ABMTR-estimated facilities that actually process peripheral blood (as opposed to bone marrow) is uncertain. For the purposes of this analysis, FDA has assumed that 400 peripheral blood stem/progenitor cell facilities will be affected by this final rule.

Although there is no single national organization that keeps track of the number of facilities for umbilical cord blood banking, FDA estimates that there are approximately 25 umbilical cord blood banks currently operating in the United States. These facilities may also seek accreditation through AABB or FACT. Based on this information, the agency estimates that a total of 425 establishments involved in manufacturing hematopoetic stem/progenitor cells would be affected by this rule.

In addition, 67 establishments produce licensed biological products or approved medical devices that are currently required to register under parts 207 and 807 (21 CFR parts 207 and 807) but would also be subject to the provisions of this final rule.

Finally, this final rule also applies to facilities involved with reproductive tissue, primarily semen banks and ART facilities that collect and process donor semen or donor oocytes. The American Society of Reproductive Medicine (ASRM) has a membership of approximately 400 fertility centers, 370 of which have provided reports to the 1999 Society for Assisted Reproductive Technology (SART) registry. The ASRM also has a 1996 list of approximately 110 semen banks operating in the United States. Although ASRM has published guidelines for donor screening and other aspects of oocyte donation, and for therapeutic donor insemination (TDI), ASRM does not exercise oversight or provide accreditation of facilities that collect donor reproductive tissue or use these tissue products in infertility treatment.

C. Nature of the Impact

This final rule includes requirements for donor screening, donor testing, recordkeeping, and quarantine of cells and tissue. Donor screening will involve the review of relevant medical records to include a medical history interview (particularly pertaining to communicable disease risk), a current report of a physical assessment for cadaveric donors, and a physical examination for living donors. For living, repeat anonymous semen donors, a complete donor-eligibility determination procedure will be required at least once every 6 months. This final rule requires that a donor specimen be tested for evidence of infection due to relevant communicable disease agents and diseases, with testing conducted within a specified time of recovery of cells or tissue. In general, a donor may be determined eligible if free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases, and if the required testing is negative or nonreactive.

This final rule also requires recordkeeping for donor-eligibility determinations. Manufacturers must ship HCT/Ps accompanied by documentation of donor eligibility status, including a summary of records that includes the results of the required testing and the name and address of the establishment that made the eligibility determination. This final rule also requires that HCT/Ps be quarantined until a donor-eligibility determination is made, and that products be clearly labeled as under quarantine during that period. Manufacturers are responsible for the appropriate labeling and documentation of HCT/Ps from a donor who is found to be ineligible.

The economic impact of these requirements is expected to be minor because the leading industry associations have already established standards for screening, testing and recordkeeping that, in most cases, meet or exceed the criteria specified in this final rule, and because existing FDA regulations already apply to certain HCT/Ps intended for transplantation (see part 1270). Table 1 of this

document lists the types of HCT/Ps that will be affected by this final rule and the associated establishments that manufacture these products. Table 1 also provides estimates of the number of establishments affected by this final rule and the estimated percentage of establishments believed to be following current industry standards for donor screening and testing. The lists of specific donor screening and testing requirements proposed by FDA can be compared with those currently required by the industry associations.

TABLE 1.—TYPE AND NUMBER OF ESTABLISHMENTS AFFECTED AND PERCENTAGE ALREADY IN COMPLIANCE WITH INDUSTRY STANDARDS FOR DONOR ELIGIBILITY SCREENING AND TESTING

Type of Human Tissue	Type of Entities Affected (and Estimated Total Number)	FDA Regulatory Requirements Compared to Industry Standards		Estimated Percent of Entities in Compliance With Industry Standards
		FDA	Industry Standards	
NonreproductiveTissue				
Eye tissue	134 FDA registered eye tissue facilities, including 93 EBAA accredited eye banks (134 total)	21 CFR part 1270 and (s1,s2,s3)[1] and (t1, t2, t3, t5)[2]	EBAA (s1 through s3)[1] and (t1 through t3)[2]	100%
Pericardium, dura-mater, heart valves, skin allograft, bone allograft, other viable	166 FDA registered tissue banks, including 75 AATB accredited tissue banks (166 total)	21 CFR part 1270 and (s1 through s3)[1] and (t1, t2, t3, t5)[2]	AATB (s1 through s3)[1] and (t1 through t5)[2]	100%
Stem progenitor cells; peripheral blood	178 FDA registered facilities, 92 NMDP donor centers, and 113 NMDP collection centers (400 total)	(s1 through s3)[1] and (t1 through t6)[2]	AABB/FACT (s1 through s3)[1] and (t1 through t6)[2]	100%
Stem progenitor cells; umbilical cord blood	Cord blood banks (25 total)	(s1 through s3)[1] and (t1 through t6)[2]	AABB/FACT (s1 through s3)[1] and (t1 through t6)[2]	100%
Licensed biological products and approved medical devices	67 FDA registered establishments (67 total)	Currently regulated under sections 351 and 361 of the PHS Act, 21 CFR parts 207 and 807		100% compliance with 21 CFR parts 207 and 807
Total	792 Facilities			
ReproductiveTissue				
Donor oocytes, embryos	370 ART facilities and associate labsin the 1999 SART report (400 total)	(s1 through s3)[1] and (t1, t2, t3, t5)[2]	ASRM/CAP (s1)[1] and (t1,t2,t3,t5)[2]	Unknown
Donor semen	4 Semen banks in 1996 AATB survey (110 total)	(s1 through s3)[1] and (t1 through t8)[2]	AATB (s1 through s3)[1] and (t1 through t8)[2] and ASRM (s1)[1] and (t1, t2, t3, t5, t7, t8)[2]	Unknown
Total	510 Facilities			

[1] Screening for: s1: HIV, s2: hepatitis, s3: CJD
[2] Laboratory Tests: t1: anti-HIV-1-2, t2: anti-HCV, t3: HBsAg, t4: anti-HTLV-I, t5: syphilis, t6: CMV, t7: *Neisseria gonorrhea*, t8: *Chlamydia trachomatis*

Based on communications with representatives of several industry associations and facility managers, FDA estimates that the number of facilities currently in compliance with industry standards for donor screening and testing approaches 100 percent for several affected types of HCT/Ps. Facilities handling reproductive tissue are the primary exception to this finding, and also represent the greatest area of uncertainty for this analysis. There is currently no single reliable source of information on fertility center or semen bank adherence to AATB standards or ASRM guidelines. A small percentage of semen banks are members of the AATB and are known to follow that organization's requirements for screening and testing, but little is known about the standards used at other facilities.

In addition to the required donor screening and testing, this final rule will require facility staff time to align current quarantine, labeling, and recordkeeping systems with the new requirements. As shown in table 2 of this document, all of the industry associations already specify requirements for these procedures. With the exception of facilities handling reproductive tissue, the current industry standards adopted by most facilities are at least as stringent as those included in this final rule.

TABLE 2.—CORRESPONDENCE OF FDA REQUIREMENTS TO CURRENT INDUSTRY STANDARDS FOR SPECIMEN QUARANTINE, LABELING, AND RECORD RETENTION

FDA	AATB	EBAA	AABB	FACT	ASRM
Quarantine	X[1]	X[1]	X[1]	X[1]	X[1]
Labeling	X[1]	X[1]	X[1]	X[1]	X[1]
Record Retention	X[1]	X[1]	X[1]	X[1]	Recommended; not required

[1] X means corresponds.

Due to the disparity in the amount of available information and the potential impact of the rule on nonreproductive versus reproductive tissue establishments, these two broad categories of tissue establishments are treated separately in the cost impact analysis that follows.

1. Impact on Nonreproductive Tissue Establishments

a. *Impact of donor screening and testing.* As summarized in table 1 of this document, most nonreproductive tissue establishments are believed to be already in compliance with FDA's new donor screening and testing requirements, as a result of following their own industry association standards and current FDA regulations. Therefore, the cost of compliance with these provisions will be minimal for these establishments.

b. *Impact of recordkeeping and tissue quarantine.* The burden of recordkeeping and tissue quarantine requirements will reflect the staff time needed to compare current recordkeeping and facility procedures with those required under the new standards and to make modifications where needed in current facility SOPs related to these activities. Such changes are expected to be minor for most nonreproductive tissue establishments.

In the proposed rule, FDA estimated that it would take approximately 8 to 40 hours to compare the new regulations against a facility's current SOPs and make any necessary modifications. Since we received no comments from affected entities, we have retained this assumption. This process will be performed by a staff person who acts as a regulatory reviewer, a supervisor, or a manager of quality assurance. Assuming a labor cost of $40 per hour (Ref. 23), this standards reconciliation effort will result in a one-time cost per facility ranging from $320 to $1,600. Applying this range of cost per facility to the approximately 792 nonreproductive tissue facilities yields an impact that ranges from $253,440 (= $320 x 792) to $1,267,200 (= $1,600 x 792).

2. Impact on Reproductive Tissue Establishments

a. *Impact of donor screening and testing.* As indicated in table 1 of this document, the number of reproductive tissue facilities currently following industry standards is unknown. Thus, FDA cannot develop a precise estimate of regulatory costs. To generate an upper bound cost estimate, however, FDA assumed that 100 percent of facilities involved with oocyte donation and 80 percent of semen banks would need to perform additional screening and testing. Although semen banks not currently following voluntary industry standards constitute a majority of the firms in that industry, they are primarily small operations that are estimated to serve only 5 percent of all semen donors.

i. *Oocyte donor screening and testing.* The estimated impact of this final rule on establishments involved in oocyte donation is based on 1999 data reported by SART, an organization of assisted reproductive technology providers affiliated with ASRM. In 1999, donor oocytes were used in approximately 10.4 percent of the 86,822 ART cycles reported, or 9,066 cycles (Ref. 4). FDA believes that all infertility treatment centers already conduct medical exams and history taking and perform some laboratory testing before oocyte retrieval for any potential donor. Compliance with this final rule, however, may entail further blood testing and adding some additional screening questions to the interview.

The cost of additional blood work (including HIV 2, HTLV I and II, and CMV IgG and IgM) is estimated at approximately $238.40 per donor (Ref. 22). The additional time to interview and record information in donor screening is estimated to cost about $37, based on the assumption that approximately half of the required screening is already being done, and that the estimated cost of a full health history interview is $75 ($37 = $75/2) (Ref. 6). Thus, the additional cost per oocyte donation is estimated at $275.40 ($238.40 + $37). Based on a reported (average) cost estimate of $13,500 (Ref. 22) per donor oocyte cycle, this translates into a 2.04 percent increase ($275.40/$13,500) in the average cost of therapy per cycle.

The cost of screening and testing oocyte donors will depend on the number of donor cycles attributable to each screened donor. If each donor contributes oocytes for only one cycle, and the rejection rate is low (assumed to be 0.57 percent, which is the estimated prevalence rate of HBsAg positivity among parturient women) (Ref. 7), the number of donors to be tested would be 9,118 (9,066/(1–0.0057)). If each donor contributes oocytes for two donor cycles, the number of donors to be screened would be 4,559. These alternative assumptions imply a total cost to U.S. facilities involved in oocyte donation of from $1,255,549 to $2,511,097 per year, as shown in table 3 of this document.

TABLE 3.—ALTERNATIVE OOCYTE DONATION SCENARIOS AND ASSOCIATED DONOR SCREENING AND TESTING COSTS

Screening and Testing Cost per Donor	2 ART Cycles per Donor = 4,559 Donors	1 ART Cycle per Donor = 9,118 Donors
$275.40	$1.26 million[1]	$2.5 million[2]

[1] $275.40 x 4,559 = $1,255,549
[2] $275.40 x 9,118 = $2,511,097

FDA believes that much of the additional screening and testing identified in table 3 of this document is already being performed by ART clinics. Therefore, these estimates should be viewed as maximum expected cost burdens. Furthermore, certain methods of donor oocyte recovery, e.g., laparoscopy, are not directly connected with the transmission of sexually transmitted and genitourinary diseases and, therefore, testing for *Neisseria gonorrhea* and *Chlamydia trachomatis* would not be required under this final rule. Use of such methods would be

expected to lower the estimated testing costs by approximately $40 per oocyte donor.

ii. *Semen donor screening and testing.* The agency has conducted an extensive search for current information on the extent of infectious disease screening for semen donors, but has found little information available. The Congressional Office of Technology Assessment (OTA) conducted a survey of establishments involved in semen donation in 1987, and found that all commercial banks surveyed performed routine screening and testing for HIV, but only 45 percent of private physicians included this screening. The most recent available data includes a list of approximately 110 commercial semen banks developed by ASRM in 1996, and a 1996 registration survey of the AATB that includes data for 4 semen banks. Some semen banks that have applied, but are not yet accredited members of AATB, are nonetheless following AATB standards. It is also likely that some other facilities have informally adopted AATB standards. This analysis assumes that all semen banks currently perform HIV screening and testing, as reported by OTA in 1987, and that a smaller percentage of facilities additionally follow all AATB screening and testing standards.

Based on conversations with semen banking industry experts, FDA estimates that the 20 largest semen banks account for approximately 95 percent of the commercial production of donor semen, and are following AATB standards for donor screening and testing. The agency analysis therefore assumes that the 20 largest facilities will experience minimal impact, while the remaining 90 facilities, which account for approximately 5 percent of total industry production, will be more significantly affected. These very small semen banks are described by an industry expert as typically functioning within a physician office practice (e.g., that of an obstetrician or gynecologist). The semen banking in these facilities is generally offered as an additional service to patients receiving fertility treatment, and is not the primary line of business within these establishments.

The total estimated cost of the proposed screening and testing requirements for semen banking facilities is based on the number of semen donors who would require screening and testing, and their respective unit costs. Due to the lack of data on the actual number of semen donors, the agency estimated the number based on projected TDI demand. The level of TDI demand has likely decreased over time, with advances in treatment for male factor infertility. For example, the development of intracytoplasmic sperm injection (ICSI) used in conjunction with in vitro fertilization (IVF) has enabled some couples to forego TDI in favor of ICSI using the male partner's sperm (Ref. 8). In 1985, an estimated 70,000 women per year received TDI (Ref. 9), compared to an estimated 171,000 women who reported ever receiving artificial insemination with donor semen in the National Survey of Family Growth (NSFG) conducted in 1995. If the NSFG respondents referred only to experience over the past 5 years, this would translate to approximately 34,200 women receiving TDI per year. Assuming an average of three cycles of therapy per patient per year, these data yield an estimated demand for TDI donor units of approximately 102,600 units per year. This figure is consistent with an industry expert estimate of current U.S. TDI production of 100,000 units per year.

The clinical literature indicates that most semen donor attrition occurs before the blood testing stage of the donor-eligibility determination. For example, in one study of donor recruitment in which the clinic followed AATB and ASRM standards, of the total of 199 potential donors initially recruited, 174 were rejected; 172 of whom were rejected before blood testing, with only 2 (1 percent) rejected based on the blood test results (Ref. 10). For the purposes of this analysis, the agency assumes that the number of donors who will require infectious disease testing is approximately equal to the number of donors needed to supply the level of demand for TDI. Thus, FDA's estimate is based on the previous TDI unit demand combined with the maximum number of births per donor suggested in ASRM guidelines (Ref. 11), the average delivery rate per cycle of intrauterine insemination, an assumed 10 donated specimens per donor per year, and 4 donation units per donor specimen (Ref. 12). These factors yield an estimated 2,565 donors required per year. Assuming that the number of donors already screened and tested is proportionate to the volume of production accounted for by facilities compliant with AATB standards, FDA estimates that approximately 5 percent of all donors, or 128 donors per year (128 = 0.05 x 2,565), may need to be newly screened and tested to meet the requirements of this final rule.

The screening cost per semen donor is assumed to include an initial medical history and physical, a 6-month followup exam, and an abbreviated screening at the time of each donation. Based on rates published on the Internet (Ref. 6), the agency estimates that a full medical exam costs $175, a less extensive followup exam will cost approximately $75 (a published fee for a health history review), and the abbreviated screening at the time of each donation will cost approximately $15 (i.e., one-fifth of the time required for a full history review). One repeat donor visit per year is assumed. Thus, the total cost of this screening is estimated to be $265 per year per donor.

The lab tests for prospective semen donors include those listed in table 1 of this document, with 6-month followup blood tests. The cost of additional testing, based on screening test fees published on the Internet (Ref. 5), is $230.16 for initial complete blood testing, plus $123.40 for followup blood testing after a 6-month quarantine period, plus $113.30 for bacterial testing. Thus, the total cost of the additional lab work is estimated to be $467 per donor per year ($230.16 + $123.40 + $113.30 = $466.86). Because these estimates are based on charges to facility clients, they are likely to represent an upper bound on actual facility costs. Using these figures, the estimated total industry cost per year is approximately $94,000 (128 x ($265 + $467) = $93,696).

b. *Impact of donor recordkeeping and tissue quarantine.* The impact of recordkeeping and tissue quarantine requirements for reproductive tissue establishments will reflect the staff time required for the following: (1) A one-time review and modification of current SOPs to bring them into alignment with the new standards, and (2) ongoing, expanded practices for each donor who undergoes screening and testing to meet the requirements of this final rule.

In the proposed rule, FDA estimated that the one-time review and alignment of current facility SOPs will require approximately 8 to 40 hours at each facility. Since we received no comments from affected entities, we have retained this assumption. As with nonreproductive tissue facilities, this process would be performed by a regulatory affairs analyst, a supervisor, or a manager of quality assurance. Assuming a labor cost of $40 per hour (Ref. 23), this standards reconciliation effort would result in a one-time cost per facility ranging from $320 to $1,600. Applying this range of cost per facility to the 400 ART clinics and 110 semen banks yields a potential one-time cost for all reproductive tissue facilities that ranges from $163,200 ($320 x (400 + 110)) to $816,000 ($1,600 x (400 + 110)).

The estimated cost of the recurring requirements for tissue quarantine,

labeling, recordkeeping and record retention at reproductive tissue facilities are based on the estimated staff time needed to create and retain records of medical history, screening information and lab testing for each prospective donor from whom specimens are collected. These records must comply with the requirements of this final rule and are estimated to require approximately 4 hours per donor per year of clerical staff time. Assuming a labor cost of $24 per hour (Ref. 24) for clerical staff time implies a cost of $96 per donor per year. Table 4 of this document summarizes the potential range of recurring costs for all reproductive tissue facilities. As shown in table 4 of this document, the estimated costs range from approximately $450,000 to $888,000, depending on the assumed number of oocyte donors.

TABLE 4.—RANGE OF RECURRING COSTS FOR REPRODUCTIVE TISSUE

128 semen donors and 4,559 oocyte donors (2 ART cycles per donor)	$449,952[1]
128 semen donors and 9,118 oocyte donors (1 ART cycle per donor)	$887,616[2]

[1] $449,952 = (128 + 4,559) x $96
[2] $887,616 = (128 + 9,118) x $96

The range of these estimates reflects the agency's current lack of information about typical donor practices for ART facilities. If a higher rate of donation per donor is typically achieved by facilities compared to that assumed in this analysis, the cost burden may be much lower than these estimates would indicate. More generally, if the current level of facility donor screening, testing and recordkeeping is more stringent among reproductive tissue facilities than assumed in this analysis, the overall cost of compliance with this final rule will also be lower than these estimates suggest.

Uncertainty about current practices results in range estimates of the cost impact of this final rule. However, because facilities in most HCT/P industry sectors already follow voluntary industry standards requiring donor screening and testing, the overall impact is expected to be minor. Tables 5 and 6 of this document provide a summary of the expected cost impacts across the different industry sectors included in the analysis. Table 5 of this document presents costs annualized at 7 percent interest over 10 years, whereas table 6 of this document presents annualized costs for the same time period using a 3 percent interest rate. The total annualized cost for the 792 nonreproductive tissue facilities is estimated to range from $30,000 to $180,000, reflecting agency uncertainty about the extent of effort necessary for a one-time review and alignment of existing SOPs with the donor screening and testing provisions of this final rule. This translates into an average annualized cost of $38 ($30,000/792) to $228 (180,000/792) per facility.

The total annualized cost of compliance for the ART industry ranges from approximately $1.71 to $3.5 million, reflecting uncertainty about the number of oocyte donors, the number of ART cycles per donor per year and current screening, testing and recordkeeping practices. These costs translate into an average annualized cost of approximately $4,270 ($1.708 million/400) to $8,693 ($3.5 million/400) per facility. In general, assumed higher rates of donation per donor, or a lower number of total donor cycles per year, will result in lower industry costs. Similarly, lower rates of donation per donor, or a greater number of total donor cycles per year, will result in higher industry compliance costs.

The total annualized cost impact on the semen banking industry is based on an estimated TDI demand of approximately 103 thousand units per year, and assumed current compliance of the top 20 commercial banks which account for approximately 95 percent of industry production. The total annualized costs range from approximately $110,000 to $131,000. These industry totals yield an average annualized cost range of $1,222 ($110,000/(110–20)) to $1,456 ($131,000/(110–20)) per facility currently noncompliant with this final rule.

TABLE 5.—SUMMARY TABLE OF DONOR ELIGIBILITY COST ANALYSIS AT 7 PERCENT INTEREST OVER 10 YEARS[1]

Type of Facility	Total One-time Cost	Total Recurring Cost	Total Annualized Cost
NonreproductiveTissue			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $253 to $1,267	Minimal Minimal	Minimal $36 to $180
Reproductive Tissue, ART Facilities			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $128 to $640	$1,255 to $2,511 $438 to $875	$1,255 to $2,511 $456 to $966
ART subtotal	$128 to $640	$1,693 to $3,386	$1,711 to $3,477
Reproductive Tissue, Semen banks			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $35 to $176	$94 $12	$94 $17 to $37
Semen subtotal	$35 to $176	$106	$111 to $131
Total Tissue Industry	$416 to $2,083	$1,799 to $3,492	$1,858 to $3,788

[1] All figures in thousands of dollars.

TABLE 6.—SUMMARY TABLE OF DONOR ELIGIBILITY COST ANALYSIS AT 3 PERCENT INTEREST OVER 10 YEARS[1]

Type of Facility	Total One-Time Cost	Total Recurring Cost	Total Annualized Cost
Nonreproductive Tissue			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $253 to $1,267	Minimal Minimal	Minimal $30 to $149
Reproductive Tissue, ART Facilities			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $128 to $640	$1,255 to $2,511 $438 to $875	$1,255 to $2,511 $453 to $950
ART subtotal	$128 to $640	$1,693 to $3,386	$1,708 to $3,461
Reproductive Tissue, Semen banks			
(a) Donor screening and testing (b) Recordkeeping and quarantine	Minimal $35 to $176	$94 $12	$94 $16 to $33
Semen subtotal	$35 to $176	$106	$110 to $127
Total Tissue Industry	$416 to $2,083	$1,799 to $3,492	$1,848 to $3,737

[1] All figures in thousands of dollars.

D. Benefits of the Final Rule

The risks of disease transmission vary by type of HCT/P. Thus donor screening, testing, and other measures to reduce the risks of transmission for various types of tissue will correspondingly yield a different relative reduction in disease risk. For example, expansion of blood donor screening and improved laboratory testing has dramatically reduced the risk of blood transfusion-transmitted disease. The risk of HIV infection has dropped from a reported 1 in 100 units in some U.S. cities to approximately 1 in 1,930,000 units. The risk of transmission of HBV has been reduced from 1 in 2,100 to 1 in 137,000 units, and the transmission risk for HCV has been lowered from 1 in 200 units in the early 1980s to the current level of 1 in 1,000,000 units (Ref. 25). The levels of risk reduction associated with blood donation offer an illustration of the kind of improvements in safety that might be achieved through improved and expanded screening and testing of HCT/P donors.

As described earlier in this document, most nonreproductive tissue establishments are assumed to be already compliant with this final rule and, therefore, have already achieved much of the potential risk reduction. However, some reduction in communicable disease transmission risk may still be realized under this final rule for firms that are not currently in compliance with the voluntary standards established by their respective professional associations. The discussion of benefits resulting from this final rule will focus on some key areas of risk and the potential benefit of the new requirements for reproductive tissue recipients. The discussion that follows will consider the risks of transmission of disease that will be reduced through expanded screening and testing among reproductive tissue donors, focusing on two life threatening chronic diseases that can be transmitted through donor tissue: HBV and HCV.

The expansion of screening among reproductive tissue donors is expected to produce important reductions in the risk of disease transmission, as evidenced by the apparent reductions in HIV risk that have already been achieved through screening. The risk of HIV transmission through TDI appears to be very low since screening for HIV was recommended by CDC in 1985. A total of six documented and two possible cases have been reported to the CDC as of December 1996 (Ref. 9).

The risks of transmitting HBV and HCV through reproductive tissue might also be substantially reduced as a result of donor screening, based on the significance of self-reported risk factors as predictors of the findings of blood screening for HBV and HCV (Refs. 13 and 14). Compared to HCV, HBV presents a greater risk of sexual transmission. In 1991, heterosexual activity was reported to account for 41 percent of all cases of HBV (Ref. 15). HBV transmission has also been reported by way of TDI. In 1982, a physician used semen from an unscreened donor (later found to be carrying HBsAg) to inseminate several women, one of whom later developed HBV (Ref. 16).

HBV-infected mothers can transmit the disease to their infants. Forty-two percent of infants born to women with HBsAg positivity (adjusted for HBeAg status) are at risk of HBV infection, and an additional 30 percent of infants born to HBsAg positive mothers become infected between 1 and 5 years of age. Prospective studies of infected infants and young children indicate that 25 percent will die from primary hepatocellular carcinoma (PHC) or cirrhosis as adults. The lifetime medical cost per case of PHC and cirrhosis is estimated to be $96,500 (Ref. 17). An analysis of the cost-effectiveness of prenatal screening and testing of mothers, with vaccination for positive screens, estimates that such screening and intervention would prevent 69 percent of the chronic HBV infections acquired perinatally or later in life (Ref. 18). This rate of effectiveness may provide an indication of the potential benefit of HBV screening required by this final rule.

The risk of transmission is estimated to be lower for HCV, compared to HBV. The CDC estimates the rate of sexual transmission between female to male partners, and the rate of transmission from mother to child, to each be approximately 5 percent. However, there is no vaccine intervention available for HCV, although interferon-alpha therapy has been found effective in eliminating the virus for at least some patients, and drug combinations (e.g.,

Interferon and Ribavirin) have been found to be even more effective. Although most patients infected with HCV are relatively healthy during most of their lives, an estimated 30 percent of those infected will eventually die of liver-related causes; an estimated 8,000 patients per year (Ref. 17). The average cost of care per year for persons with liver disease from chronic HCV is estimated to range from $24,600 for patients without interferon-alpha therapy to $26,500 per year for those receiving a 12-month course of therapy. The latter is estimated to provide patients with an additional 0.37 quality-adjusted life-years (QALYs) (Ref. 18).

Screening reproductive tissue donors is expected to significantly reduce the excess morbidity and mortality associated with HBV and HCV. As noted previously in this document, there are an estimated 4,559 to 9,118 oocyte donors and 2,565 semen donors per year. If these populations experience recently reported prevalence rates for HCV (1.8 percent) and HBV (4.9 percent) (Refs. 13 and 14), then screening for significant risk factors and disease markers will result in reduced HBV and HCV exposures for the patient population at risk. The population at risk each year is estimated to include 3,022 to 9,066 women undergoing IVF with donor eggs, and 2,285 newborns delivered as a result of this therapy[1]; and 34,200 to 70,000 women receiving TDI, and 8,800 newborns delivered as a result of that therapy.

E. Small Entity Impacts and Analysis of Alternatives

Based on its analysis, FDA found that a substantial number of the establishments required to comply with this final rule may be small business entities. The Small Business Administration defines a small business in this industry sector (NAICS code 621991, Blood and Organ Banks) to be an establishment with $8.5 million or less in annual receipts (Ref. 19). The economic impact analysis presented in section IV.C of this document includes estimates of the number of entities to which this final rule will apply. Each sector of the tissue banking industry includes some facilities that would be classified as small business entities.

A 1995 study of conventional tissue banks (Ref. 20) reports average annual revenues of $1.23 million per facility, which translates into $1.45 million per facility (in 2002 dollars) based on inflation data reported by the Bureau of Labor Statistics. Most nonreproductive tissue facilities are assumed to have a comparable level of average revenues. Reproductive tissue industry experts estimate that 65 percent of ART facilities have average revenues of approximately $2.5 million per year and the remaining 35 percent have average revenues of $11.5 million per year. Industry experts also estimate that 19 of the 20 largest semen banks have average annual revenues of approximately $2 million per year, and 1 of the 20 largest facilities has annual revenues greater than $8.5 million. Thus, the vast majority of facilities in each HCT/P industry sector are small entities. Nevertheless, as noted in the preceding cost analysis, most of these facilities will not be significantly impacted by this final rule because they are already meeting the infectious disease screening and testing and recordkeeping requirements.

Table 7 of this document presents estimates of the average annualized cost per affected small facility expressed as a percentage of average annual revenues. In addition to facility revenues, table 7 presents the estimated annual revenue for physician-owned obstetrician/gynecologist (ob/gyn) practices, because some operate a small donor semen bank as an additional service to patients, but may not currently comply with all of the requirements of this final rule. The average annual practice revenue per self-employed physician in the ob/gyn specialty category was reported as $627,000 in 1998 (Ref. 21). This translates into $692,000 (in 2002 dollars) based on inflation data reported by the Bureau of Labor Statistics.

TABLE 7.—ESTIMATED ANNUALIZED COST PER FACILITY AS A PERCENTAGE OF ESTIMATED ANNUAL REVENUE

Number of Facilities That May Be Classified as Small Entities	Average Annualized Cost per Facility	Average Annual Revenue per Facility	Annualized Cost as Percentage of Annual Revenue
Nonreproductive Tissue			
792 (all potentially small entities)	$38 to $228	$1.45 million	0.003 to 0.016%
Reproductive Tissue, ART Facilities			
260 (65% of 400 facilities)	$4,270 to $8,694	$2.5 million	0.17 to 0.35%
Reproductive Tissue, Semen banks			
19 small commercial banks	$1,222 to $1,456	$2.0 million	0.06 to 0.07%
90 small physician practice-based banks	$1,222 to $1,456	$692,000	0.18 to 0.21%

As noted in table 7 of this document, the greatest expected cost will be incurred by facilities involved with reproductive tissue. Nevertheless, the estimated impact on most small facilities does not appear to be significant. The expected cost burden per facility ranges up to 0.35 percent of average annual revenues. However, if current practices actually involve a much lower level of infectious disease screening and testing than assumed in this analysis, the impact of the new requirements would be greater than expected.

Although this final rule will impose some costs on small entities involved in the manufacture of HCT/Ps, the agency believes that this approach represents an effective means of protecting patient safety and public health. The less burdensome alternatives to this final rule involve fewer requirements for small entities (the vast majority of facilities in the HCT/P industry), but fail to provide fundamental assurances of product safety. For example, reliance on

[1] The range of 3,022 to 9,066 patients is based on a reported 9,066 ART cycles using donor oocytes reported for 1999, varying the assumed number of cycles per patient. The number of newborns is based on an average success rate of 25.2 percent (live births per ART cycle).

published FDA guidance for donor eligibility determination, rather than establishing a regulatory requirement, would provide the agency with no basis for ensuring compliance. Thus, agency guidance may have no greater influence than current voluntary industry standards, which have similar provisions, but have failed to persuade all facilities to adopt comprehensive screening and testing practices. FDA's guidance, alone, therefore, would not be expected to provide adequate protection from the public health risks associated with infected donor-derived HCT/Ps.

Another alternative would involve waiving some of the donor screening and testing requirements for small facilities. However, as noted previously, the vast majority of facilities in this industry are small. Moreover, this alternative would increase the safety risks associated with HCT/Ps if small facilities that currently screen and test donors on a voluntary basis choose to discontinue this practice due to an FDA-granted waiver. For example, waiving a requirement for donor screening would eliminate an extremely cost-effective first-tier level of safety protection because prospective donors deferred or disqualified at this stage need not undergo further testing. Similarly, waiving the requirements for blood testing would expose patients, as well as tissue facility medical staff, to avoidable risks of infectious disease that may be undocumented in a patient's medical history, or be unknown to, or not mentioned by the living donor or cadaveric donor's family during screening.

We also considered waiving the requirement for semen quarantine and anonymous donor retesting to detect infections during the window period, when a donor's infection may not yet be detectable by blood tests. However, this alternative would expose recipients and the public to risks from infectious disease agents that cannot be immediately detected after exposure through most currently available blood tests (e.g., tests for HIV and HCV). Recordkeeping for donor screening and testing is also critical to protecting product recipient and public safety. Adequate documentation and record retention ensure that HCT/Ps can be tracked to their source in the event of infection or other adverse reactions that result from donor tissue characteristics.

In summary, the agency believes that abridged requirements for donor screening and testing, based on voluntary standards or facility size criteria, would provide inadequate protection against the risk of infectious disease transmission through HCT/Ps. Most notably, the absence of regulation allows reproductive tissue facilities to omit the screening and testing of donors that is routinely performed for other types of HCT/Ps, thus exposing patients undergoing infertility treatment to a disproportionate risk of exposure to several life-threatening infectious disease agents.

To help alleviate the impact on small entities while still protecting public health, the agency is not requiring that manufacturers follow screening and testing procedures when an HCT/P is used in the same person from whom it is obtained, or in a sexually intimate partner of a reproductive tissue donor. The agency believes the risk of disease transmission from such activities is minimal. Further, in the case of reproductive HCT/Ps, the 6-month quarantine requirement applies only to semen from anonymous donors and not to oocytes and embryos.

As part of the development process for this final rule, FDA conducted an extensive outreach program in an effort to inform affected small entities and to request input regarding the potential economic impact. Representatives from CBER have given presentations on HCT/P donor eligibility related issues at the annual conferences of many of the professional associations representing affected entities including ASRM, AATB, EBAA, and others. The agency has also engaged in outreach activities directed toward interested consumer groups such as RESOLVE and the American Infertility Association. At their request, FDA also held individual meetings with groups such as ASRM, EBAA and AATB to discuss specific concerns regarding the impact of the donor eligibility rule. Some of these presentation materials and meeting minutes are available on the CBER Web page at *http://www.fda.gov/cber/tissue/min.htm*. Additional materials associated with the donor eligibility rule are available on the Internet at *http://www.fda.gov/cber/tissue/docs.htm*. Finally, in the proposed rule, FDA requested industry comment regarding the assumptions upon which this analysis of economic impacts was based. In particular, we requested detailed industry comment regarding our estimates of the number and type of entities affected, current donor screening and testing practices, and expected compliance costs. To the extent possible and appropriate, we have incorporated these comments and our responses into the preamble and analysis of economic impacts of this final rule.

Under this final rule, small entities involved with reproductive tissue must meet the same safety and quality standards as large reproductive tissue facilities and other HCT/P manufacturers. The specific requirements for donor screening and testing, the required recordkeeping, and the required types of professional skills are described in the economic analysis provided previously. This analysis includes an accounting of all major cost factors, with the exception of the reduced potential liability currently encountered by those reproductive tissue facilities that fail to provide the level of protection from infectious disease that is considered a standard of good practice in other sectors of the HCT/P industry. The relevant Federal rules that are related to this final rule are discussed in section II of this document. This economic analysis provides a summary of the voluntary industry standards that overlap this final Federal standard, but as discussed, there is no current regulation of HCT/Ps that will duplicate this final rule. Consequently, FDA finds that this final rule will enhance both public health and public confidence in the safety and utility of HCT/Ps, while imposing only a minimum burden on the affected industry sectors.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) and (j) that this action is of a type that is categorically excluded from the preparation of an environmental assessment because these actions, as a class, will not result in the production or distribution of any substance and therefore will not result in the production of any substance into the environment.

VI. Federalism Assessment

Executive Order 13132, dated August 4, 1999, establishes the procedure that Federal agencies must follow when formulating and implementing policies that have federalism implications. The Executive order described nine fundamental federalism principles, stressing the importance and sovereignty of State and local governments, and the contributions of individual States and communities to the development of enlightened public policy. Principles of federalism are inherent in the very structure of the Constitution and formalized in and protected by the Tenth Amendment. Regulations have federalism implications whenever they have a substantial direct effect 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. Whenever a regulation has this result, the agency must prepare a federalism assessment.

The Executive order directs Federal agencies to:

1. Encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States;

2. Where possible, defer to the States to establish standards;

3. In determining whether to establish uniform national standards, consult with appropriate State and local officials as to the need for national standards and any alternatives that would limit the scope of national standards or otherwise preserve State prerogatives and authority; and

4. Where national standards are required by Federal statutes, consult with appropriate State and local officials in developing those standards.

This final rule establishes donor-eligibility and other related requirements for HCT/P establishments. In issuing this rule, we rely on the authority of section 361 of the PHS Act (42 U.S.C. 264), under which 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. (We also rely on our authority to issue CGMP regulations to amend the existing CGMP regulations for drugs in 21 CFR parts 210 and 211, which include CGMP requirements, to incorporate the testing and screening provisions of part 1271 subpart C for HCT/Ps regulated as drugs, and/or biological products (see e.g., 21 U.S.C. 351(a)(2)(B)).

The donor-eligibility proposed rule was published after Executive Order 13132 was issued, but before it went into effect. Nevertheless, we made a considerable effort after the publication of the proposed rule to ensure that States had the opportunity to review the proposed rule and submit comments on it. We directed a mailing of the proposed rule to State health officials to encourage their comments on the proposed rule. We also sent copies of the rule to each State attorney general. To provide additional time to the States to comment on the proposed rule, we reopened the comment period.

In the **Federal Register** document reopening the comment period, we noted that we had learned that several States had enacted legislation and issued regulations governing tissue donor suitability (65 FR 20774, April 18, 2000). Because those laws might conflict with provisions in the proposed rule, we invited State officials to participate in the rulemaking. We specifically noted that we would appreciate comment on the following topics: (1) The need for uniform national standards for donor suitability determinations to prevent communicable disease transmission through human cellular and tissue-based products, (2) the scope of such proposed national requirements and their impact upon State laws, (3) FDA's proposal not to preempt State laws on legislative consent for cornea transplants, and (4) any issues raised by this proposed rule possibly affecting State laws and authorities.

We received only one comment from a State official. This comment addressed abbreviated screening, which is discussed in comment 50 of this document. The comment also asked that we require deferral records for donors determined to be unsuitable. Reviewing deferral records before each donation would only be necessary in the case of living donors who could donate more than once, such as semen donors. As part of the screening process in § 1271.75, establishments determining donor eligibility are required to review the donor's relevant medical records, which would identify the donor as an unsuitable donor. Therefore, we believe that requiring deferral records would be burdensome. We received no comments from State officials on federalism issues.

To the extent that these final regulations cover areas that are already subject to Federal regulation, rather than regulation by the States, we believe the federalism implications of this final rule are minimal or nonexistent, because national standards are already in place. Since 1993, there have been Federal regulations on human tissue intended for transplantation. These regulations, contained in part 1270 (21 CFR part 1270), govern donor screening, testing, and other related issues. The regulations now being made final replace the regulations in part 1270. Although the new donor-eligibility regulations are more extensive in their requirements, and apply to a greater range of HCT/Ps, many of the establishments that will be required to comply with this final rule have been subject to the regulations in part 1270 or to drug or device regulations.

However, we acknowledge that this final rule will have an effect in those areas where there has been no uniform Federal regulation. For example, this rule sets out testing and screening requirements for donors of reproductive cells and tissue, an area where there is a range of State regulation. Some of the State statutes and regulations that have come to our attention focus on the risk of HIV transmission through semen donation and are thus more limited in their requirements than this final rule, which requires testing and screening for additional communicable disease agents and diseases and does not apply only to semen (see e.g., Ind. Code 16–41–14–7; Md. Code Ann., Health-Gen. 18–334(e); 12 Va. Admin. Code 5–90–240, 5–90–250).

Directed donation of reproductive cells or tissue is another area of potential differences between State laws and regulations and this final rule, which permits the use of fresh semen from directed reproductive donors without retesting of the donor 6 months after donation. The final rule is consistent with the California Health and Safety Code with respect to directed reproductive donors, but may be inconsistent with Indiana law, which appears to require quarantine of all semen donations pending retesting 6 months after donation (see Cal. Health & Safety Code § 1644.5(c); Ind. Code 16–41–14–7). We note that Indiana's more stringent statute may coexist with this final rule.

To the extent that additional differences may exist between State statutes and regulations and this final rule with respect to reproductive cells and tissues and other areas where there has not previously been Federal regulation, we recognize that there may be a federalism impact. However, to the extent there is such an impact, it is a necessary part of our effort to institute uniform screening and testing requirements, to prevent the introduction, transmission, or spread of communicable disease.

In the proposed rule, we identified a particular area where we believed concerns about Federal preemption of State laws could arise: Legislative consent, or the recovery of corneas in accordance with State laws that allow the medical examiner or coroner to procure corneal tissue without the consent of the donor's next of kin (64 FR 52696 at 52703). The proposed rule did not contain an exception from the donor medical history interview for corneas procured under legislative consent. We recognized that, when corneal tissue is procured without the consent of the donor's next of kin, a donor medical history interview with the donor's next of kin does not necessarily occur. We noted, however, that the proposed definition of donor medical history interview would permit the interview to be conducted with an individual knowledgeable about the donor's medical history and relevant social behavior and would not require an interview with the next of kin. For that reason, we considered that the proposed

rule and State laws on legislative consent may coexist, and we stated that we did not intend at that time to preempt those laws. We requested that affected parties submit specific, detailed comments on any potential conflicts that might make it impossible to comply with both this regulation and State laws on legislative consent.

Many comments from industry opposed our proposal to require a donor medical history interview for all HCT/P donors, including donors of corneas recovered under legislative consent, and some disputed our assertion that the regulation and State laws could coexist. We address those comments in comments 45 and 46 of this document. After considering the comments, we continue to consider the donor medical history interview necessary for all donors to prevent the introduction, transmission, or spread of communicable diseases, and decline to make an exception for corneas donated under legislative consent.

Although we believe the final rule provides sufficient flexibility to allow for the continued recovery of corneas under legislative consent, we recognize that there may be some difficulty in communicating with the primary treating physician without obtaining permission from the deceased and/or the family of the deceased, and that, therefore, this final rule may have a negative effect on the ability of medical examiners and coroners to recover corneas under State legislative consent laws. However, given the potential for corneas to transmit communicable disease, including TSE, we have concluded that making an exception from the requirement for a donor medical history interview in the case of corneas obtained under legislative consent is not justified.

This final rule represents the exercise of a core Federal function: "* * * prevent[ing] the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession" (section 361(a) of the PHS Act; 42 U.S.C. 264). To prevent the transmission of communicable disease in the United States, including the interstate transmission of disease, uniform national standards on donor testing and screening are necessary. No State official commented otherwise. For these reasons, and for the reasons discussed previously in this document, this rule is consistent with the federalism principles expressed in Executive Order 13132.

VII. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that have been reviewed by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). (OMB control number 0910–0543 expires May 31, 2007.) A description of these provisions is shown as follows with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products.

Description: Under the authority of section 361 of the PHS Act, FDA is requiring HCT/P establishments to screen and test the donors of cells and tissue used in those products for risk factors for and clinical evidence of relevant communicable disease agents and diseases. FDA is requiring that donor-eligibility determination regulations apply to all establishments described in § 1271.1(b). The documented determination of whether a donor is eligible or ineligible is made by a responsible person and is based on the results of required donor screening, which includes a donor medical history interview (§ 1271.3(n)), and testing (§ 1271.50(a)). HCT/P establishments are permitted to ship an HCT/P only if it is accompanied by documentation of the donor-eligibility determination (§ 1271.55(a)). This requirement applies to an HCT/P from a donor determined to be eligible as well as to a product from a donor who is determined to be ineligible and made available for use under certain provisions. The accompanying documentation must contain a summary of records used to determine donor eligibility, and a statement whether, based on the results of the screening and testing of the donor, the donor is determined to be eligible or ineligible.

Records used in determining the eligibility of a donor, i.e., results and interpretations of screening and testing, the donor eligibility determination, the name and address of the testing laboratory or laboratories, and the name of the responsible person who made the determination and the date, must be maintained (§ 1271.55(d)(1)). If any information on the donor is not in English, the HCT/P establishment must retain the original record and the statement of authenticity from the translator (§ 1271.55(d)(2)). HCT/P establishments must retain the records pertaining to HCT/Ps at least 10 years after the date of administration, distribution, disposition, or expiration, whichever is latest (§ 1271.55(d)(4)).

When a product is shipped in quarantine, before completion of screening and testing, the HCT/P establishment must provide the donor identification, a statement that the donor-eligibility determination is not completed and that the product is not to be used until eligibility determination is completed (§ 1271.60(c)). With the use of a product from an ineligible or incompletely tested donor the following information must accompany the HCT/P: The results of any completed donor screening and testing, and a list of any required screening and testing not completed. When using an HCT/P from an ineligible donor, documentation by the HCT/P establishment is required showing that the recipient's physician received notification of the screening and testing results (§§ 1271.60(d)(3) and 1271.65(b)(3)).

An HCT/P establishment also is required to establish and maintain procedures for all steps that are performed in determining eligibility (§ 1271.47(a)), including the use of a product from a donor testing positive for CMV (§ 1271.85(b)(2)). The HCT/P establishment must record any departure from the procedures (§ 1271.47(d)).

These provisions are intended as safeguards to prevent the transmission of communicable diseases that may occur with the use of cells and tissue from infected donors. Through this action FDA will improve its ability to protect public health by controlling the spread of communicable diseases.

Description of Respondents: HCT/P establishments.

As required by section 3506(c)(2)(B) of the PRA, we provided an opportunity for public comment on the information collection requirements of the proposed rule (64 FR at 52715). Under the PRA, OMB reserved approval of the information collection burden in the proposed rule stating that they will make an assessment in light of public comments received on the proposed rule. One comment on the information collection burden was submitted to the docket.

(Comment 99) One comment states that, although FDA invites comments on whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility, there are no data supporting any practical utility of the information collection, and that the

estimated burden of the proposed collection of information is extremely low compared to the actual cost.

(Response) The reporting and recordkeeping information collection burdens are necessary to help ensure that the objective of the regulations (i.e., to prevent the transmission of communicable disease), is fulfilled. This provides information to the consignee or user of the product that the donor of the product was adequately and appropriately screened and tested for evidence of specific disease agents. In addition, this information allows FDA to monitor the compliance of HCT/P establishments with the regulations.

The data described in section V of the proposed rule is not for the purpose of supporting the practical utility of the information collection, but for demonstrating how the burden is calculated. Although the comment states that the calculated burden is low, the comment did not offer additional data in support of the comment.

We estimate the burden of this collection of information as follows:

TABLE 8.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.3(n)	1,302	60	78,136	1.0	78,136.0
1271.55(a)	1,235	787	972,417	0.5	486,208.5
1271.60(c)	1,069	208	222,417	0.5	111,208.5
Total					675,553.0

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 9.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Record-keepers	Annual Frequency per Record-keeping	Total Annual Records	Hours per Record	Total Hours
One-Time Burden (Creation of SOPs) 1271.47(a) and 1271.85(b)(2)	510	5	2,550	16	40,800
One-time Burden (Review of existing SOPs for compliance)	792	5	3,960	8	31,680
SOP Update	1,302	5	6,510	2	13,020
1271.47(d)	1,102	1	1,102	1	1,102
1271.55(d)(4)	195	1	195	120	23,400
1271.50(a)	510	9	4,640	5	23,200
1271.55(d)(1)	329	162.85	53,579	1	53,579
1271.55(d)(2)	1,302	1	1,302	1	1,302
1271.60(d)(3) and 1271.65(b)(3)	1,302	1	1,302	2	2,604
Total					190,687

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

In the proposed rule, we underestimated the number of respondents. Based on updated information from FDA's registration data and trade organizations, we have revised our estimate of establishments to approximately 1,302 (i.e., approximately 166 conventional tissue establishments, 134 eye tissue establishments, 425 peripheral and cord blood stem/progenitor cell establishments, 510 reproductive tissue establishments, and 67 manufacturers of products regulated under the act and section 351 of the PHS Act).

We also have adjusted our estimates for the number of HCT/Ps annually produced based on updated information from industry provided to us at the time we prepared the final rule.

Our burden estimates for the annual frequency per response and average hours per response are based on institutional experience with comparable reporting and recordkeeping provisions for biological products. These burden estimates have not changed. Also, we are adding burden estimates for §§ 1271.3(n) and 1271.47.

In estimating the burden, we compared the regulations with the current voluntary standards of a number of industry organizations, such as, AATB, EBAA, AABB, FACT, NMDP, and the College of American Pathologists, and the guidelines provided by ASRM. In those cases where a voluntary industry standard appears to be equivalent to a regulation, we assumed that any reporting or recordkeeping burden is a customary and usual business practice of HCT/P establishments who are members of those organizations and no additional burden is calculated here.

Under § 1271.3(n), approximately 1,302 establishments (166 conventional

tissue establishments, 134 eye tissue establishments, 425 peripheral and cord blood stem/progenitor cell establishments, 510 reproductive tissue establishments, and 67 manufacturers of products regulated under the act and section 351 of the PHS Act) are required to have a documented medical history interview about the donor's medical history and relevant social behavior as part of the donor's relevant medical records for each of the estimated 78,136 donors (approximately 20,000 conventional tissue donors, 47,796 eye tissue donors, 5,700 peripheral and cord blood stem/progenitor cell donors, and 4,640 reproductive cell and tissue donors). We estimate that the time to conduct the interview with the donor, if living, or with an individual able to provide the information sought in the interview, is 1 hour.

Under § 1271.55(a), 972,417 HCT/Ps (approximately 750,000 conventional tissues, 94,186 eye tissues, 6,031 hematopoetic stem/progenitor cells, and 122,200 reproductive cells and tissues) are distributed per year. The agency estimates that, for each HCT/P, 1,235 establishments (1,302–67 establishments with approved applications) will expend approximately 0.5 hours to prepare the summary of records. Conventional and eye tissue establishment are currently required to provide a summary of records under § 1270.33(d), which § 1271.55 replaces.

Under § 1271.60(c), a record consisting of donor identification and a statement that the donor-eligibility determination is not completed and that the HCT/P is not to be used until the determination is completed, must accompany each HCT/P shipped under quarantine. We estimate that approximately 1,069 establishments may ship an estimated 222,417 HCT/P under quarantine and that the preparation of the record would take approximately 0.5 hours.

We assume that approximately 510 reproductive HCT/P establishments would create 5 SOPs under §§ 1271.47(a) and 1271.85(b)(2) for a total of 2,550 records, and we estimate that it would take 16 hours per new SOP for a total of 40,800 hours as a 1-time burden. We estimate that up to 5 SOPs would already exist for 792 HCT/P establishments as a result of complying with current applicable regulations or following industry organizational standards, and that it would take each establishment approximately 8 hours per SOP to complete the review for compliance with the requirements for a total of 31,600 hours as a 1-time burden.

Once the SOPs are created, annual SOP maintenance of existing SOPs is estimated to involve 2 hours annually per SOP for all HCT/P establishments. Annual total hours for maintaining the SOPs is estimated at 13,020.

Under § 1271.47(d), an estimated 1,102 HCT/P establishments would take approximately 1 hour to annually document one departure from an SOP.

Under § 1271.55(d)(4), we estimate that 195 HCT/P establishments not currently following existing industry standards will expend 120 hours (10 hours per month) annually to maintain records for 10 years.

Under § 1271.50(a), documentation of donor eligibility is required for the first time for approximately 510 reproductive tissue establishments. Out of a total of 1,302 establishments of HCT/Ps, there would be no added burden for approximately 792 other establishments who document donor eligibility as usual and customary business practice under the trade organization standards. FDA estimates that § 1271.50(a) would impose a new collection of information requirement on 510 establishments of reproductive HCT/Ps, each of which would document the eligibility of an estimated 9 donors per year, or 4,640 donors, expending approximately 5 hours per document.

Approximately 329 HCT/P establishments would maintain screening and testing records under § 1271.55(d)(1) for an estimated 53,579 donors, which would take approximately one hour per donor.

For documents originally not in English, approximately 1,302 HCT/P establishments would maintain a record of translation with an authenticity statement by the translator and the original documents. We estimate that it would take one hour for each establishment to maintain one such document annually.

Under §§ 1271.60(d)(3) and 1271.65(b)(3), when an HCT/P that is ineligible or not fully screened or tested is used, approximately 1,302 establishments of HCT/Ps are required to document the reason for using the product, and notice of the results of testing and screening to the physician. The agency estimates that such documentation would occur approximately once annually per establishments and that each establishment would expend approximately 2.0 hours to create such document.

Under section 1320.3(c)(2) of the PRA, the labeling requirements in proposed §§ 1271.60(d)(2), 1271.65(b)(2), 1271.65(c)(1) and (c)(2), 1271.80(b)(1), (b)(2), and (b)(3) and 1271.90(b), do not constitute collection of information because information required to be on the labeling is originally supplied by FDA to the establishments for the purpose of disclosure to the public to help ensure a safe supply of HCT/Ps and protect public health.

The reporting of screening and testing results to the physician in § 1271.60(d)(4) does not constitute additional reporting burden because it is calculated under the requirement for § 1271.55(a).

The information collection requirements of the final rule have been submitted to OMB for review. Before the effective date of this final rule, we will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

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19. U.S. Small Business Administration, Office of Size Standards, Table of Size Standards, Sector 62—Health Care and Social Assistance, February 22, 2002.

20. Prottas, J., "A Study of the Tissue Procurement and Distribution System of the United States," Brandeis University, FDA/HRSA contract no. 240–090–0048, October 1995.

21. American Medical Association, Center for Health Policy Research, *Physician Socioeconomic Statistics*, 2000–2002 ed., table 41, p. 83.

22. Based on information provided by Dr. David Hoffman, NW Center for Infertility and Reproductive Endocrinology, August 2001.

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List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 820

Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 1271

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

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and 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 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

■ 1. The authority citation for 21 CFR part 210 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 2. Section 210.1 is amended by adding paragraph (c) to read as follows:

§ 210.1 Status of current good manufacturing practice regulations.

* * * * *

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in § 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

■ 3. Section 210.2 is revised to read as follows:

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

■ 4. The authority citation for 21 CFR part 211 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 5. Section 211.1 is amended by revising paragraph (b) to read as follows:

§ 211.1 Scope.

* * * * *

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts

600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

* * * * *

PART 820—QUALITY SYSTEM REGULATION

■ 6. The authority citation for 21 CFR part 820 is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383; 42 U.S.C. 216, 262, 263a, 264.

■ 7. Section 820.1 is amended by adding two sentences to the end of paragraph (a)(1), and by revising paragraph (b) to read as follows:

§ 820.1 Scope.

(a) *Applicability.* (1) * * * Manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in § 1271.3(d) of this chapter, that are medical devices (subject to premarket review or notification, or exempt from notification, under an application submitted under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act) are subject to this part and are also subject to the donor-eligibility procedures set forth in part 1271 subpart C of this chapter and applicable current good tissue practice procedures in part 1271 subpart D of this chapter. In the event of a conflict between applicable regulations in part 1271 and in other parts of this chapter, the regulation specifically applicable to the device in question shall supersede the more general.

* * * * *

(b) The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other generally applicable requirements.

* * * * *

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

■ 8. The authority citation for 21 CFR part 1271 is revised to read as follows:

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

§ 1271.1 [Amended]

■ 9. Section 1271.1 *What are the purpose and scope for this part?* is amended by removing the phrase "donor-suitability" and adding in its place the phrase "donor-eligibility" wherever it appears.

■ 10. Section 1271.3 is amended by adding paragraphs (h) through (x) to read as follows:

§ 1271.3 How does FDA define important terms in this part?

* * * * *

(h) *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.

BIOHAZARD

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

(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.

(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.

(l) *Directed reproductive donor* 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.

(m) *Donor* means a person, living or dead, who is the source of cells or tissue for an HCT/P.

(n) *Donor medical history interview means* a documented dialog 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:

(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).

(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.

(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.

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

(r) *Relevant communicable disease agent or disease* 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 gonorrhea.*

(2) A disease agent or disease not listed in paragraph (r)(1) of this section:

(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 measures 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.

(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 of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease).

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

(u) *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.

(v) *Act* means the Federal Food, Drug, and Cosmetic Act.

(w) *PHS Act* means the Public Health Service Act.

(x) *FDA* means the Food and Drug Administration.

■ 11. Part 1271 is amended by adding subpart C, consisting of §§ 1271.45 through 1271.90, to read as follows:

Subpart C—Donor Eligibility

Sec.

1271.45 What requirements does this subpart contain?

1271.47 What procedures must I establish and maintain?

1271.50 How do I determine whether a donor is eligible?

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

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

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?

1271.75 How do I screen a donor?

1271.80 What are the general requirements for donor testing?

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

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

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.

(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.

§ 1271.47 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 whether 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:

(i) Is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases; and

(ii) 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 nonreactive, 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 retain?

(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 or directed reproductive donations, 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.C. 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:

(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/P's 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 retesting required under § 1271.85(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) *Nonclinical use.* You may make available for nonclinical 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 Nonclinical 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 encephalopathy, including Creutzfeldt-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 diseases 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 ensures 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 gonorrhea.*

(d) *Ineligible donors.* You must determine ineligible a donor who is identified as having either of the following:

(1) A risk factor for or 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 6 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 1 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 at the time of recovery of cells or tissue from the donor. However, if collection at the time of recovery is not feasible, then you may collect the donor specimen up to 7 days before or after recovery or, for donors of peripheral blood stem/progenitor cells only, up to 30 days before recovery. 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 manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases; however, until such time as appropriate FDA-licensed, approved, or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhea* are available, you must use FDA-licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, 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 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 1 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 1 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 tissue, whether viable or nonviable, for evidence of infection due to relevant communicable disease agents, 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 diseases, including:

(i) Human T-lymphotropic virus, type I; and

(ii) Human T-lymphotropic virus, type II.

(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 gonorrhea.*

(d) *Retesting anonymous semen donors.* Except as provided under § 1271.90 and except for directed reproductive donors as defined in § 1271.3(l), at least 6 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 requirement of determining donor eligibility, and what labeling requirements apply?

(a) *Donor-eligibility determination not required.* You are not required to make a donor-eligibility 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; or

(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, originally exempt under paragraph (a)(1) or (a)(2) at the time of donation, that are subsequently intended for directed donation, provided that

(i) Additional donations are unavailable, for example, due to the 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.

(b) *Required labeling.* You must prominently label an HCT/P listed in paragraph (a) of this section:

(1) "FOR AUTOLOGOUS USE ONLY," if it is stored for autologous use;

(2) "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" and "WARNING: Advise patient of communicable disease risks," unless you have performed all otherwise applicable screening and testing under §§ 1271.75, 1271.80, and 1271.85; and

(3) 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)" 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.

Dated: March 10, 2004.

Lester M. Crawford,

Acting Commissioner for Food and Drugs.

Dated: March 10, 2004.

Tommy G. Thompson,

Secretary of Health and Human Services.

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