

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210, 211, 820, and 1271

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**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 [insert date 1 year after date of publication in the Federal Register]. This ~~effective date~~ <sup>rule</sup> is applicable to cells and tissues recovered on or after ~~this date~~. [insert date 1 year after date of publication in the Federal Register].

D. Balle  
5/15/04  
OK Paula  
McKenna  
Diane Seibon

NFR I

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

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### 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. sup. 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 gonorrhoea*. 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 gonorrhoea*. 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 gonorrhoea* 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 relevant 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 gonorrhoea*. 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](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 regimen, 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 gonorrhoea*, 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