

communicable disease testing. Section 1271.3(p) defines plasma dilution as a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies.

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

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

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

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

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

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

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

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

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

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

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

(Response) The calculations that are made to determine if plasma dilution has occurred depend upon the category of fluids transfused or infused. The three categories are blood (e.g., whole blood, red blood cells); colloids (e.g., dextran, plasma, platelets, albumin, hetastarch); and crystalloids (e.g., saline,

dextrose in water, Ringer's lactate). If the donor has received colloids in the 48 hours before death or specimen collection, and/or crystalloids in the one hour before death or specimen collection, then a comparison of the total volume of these fluids with the donor's plasma volume would be sufficient to determine if plasma dilution has occurred. However, when the fluids transfused are in the "blood" category (alone, or in combination with colloids and/or crystalloids), a comparison of the total volume of these fluids with the donor's blood volume should be performed, in addition to a comparison of the total volume of colloids and/or crystalloids with the donor's plasma volume.

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

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

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

include whole blood in the category of “blood” transfused in the 48 hours before death or specimen collection.

10. What Testing Is Required for Different Types of Cells and Tissues?

(§ 1271.85)

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

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

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

We have deleted the phrase “at a minimum” from § 1271.85(a), (b), and (c), because it might give the impression that testing is required only for those communicable diseases listed in § 1271.85. Although at this time we only

require testing for these diseases, in the future additional diseases may be identified as relevant. As discussed in comment 16 of this document, we will issue guidance that notifies you when we believe additional relevant communicable diseases meet the definition in § 1271.3(r)(2).

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

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

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

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

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

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

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

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

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

(Response) We disagree that syphilis testing should not be required for cell and tissue donors, including cornea donors, and note that we have not eliminated syphilis testing of blood donors. In the final rule on testing of blood donors, we noted that comments did not provide sufficient supporting data to justify eliminating the requirements to test blood and blood components with a serological test for syphilis. Moreover, preliminary results from ongoing studies indicate that the infectivity of seroreactive donors remains the subject

of scientific debate. For this reason, we maintained the syphilis testing requirement for blood donors (Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents, Final rule (66 FR 31146, June 11, 2001)).

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

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

(Comment 71) We received several comments on our proposal to distinguish between leukocyte-rich cells and tissue and other cells and tissue, and on our preamble discussion of which cells and tissues we consider leukocyte-rich (64 FR 52696 at 52705). One comment noted that the differentiation was helpful. The comment suggested adding cultures of certain cell types, such as fibroblasts, to the list of materials that are not considered to be leukocyte-rich. Two comments asserted that oocytes and embryos are not

leukocyte-rich. One comment noted that the term “stem cells,” listed in the preamble as an example of leukocyte-rich cells or tissue, is too broad, and would apply to corneal epithelial stem cells, which are not leukocyte-rich. Another comment agreed that semen can be characterized as leukocyte-rich tissue but asserted that treated or “washed” sperm do not pose the same disease risks.

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

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

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

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

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

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

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

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

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

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

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

c. Reproductive cells and tissues (§ 1271.85(c)). Proposed § 1271.85(c) would list relevant communicable disease agents and diseases of the

genitourinary tract for which you would test a donor of reproductive cells or tissue. The proposal would exclude reproductive cells or tissues procured by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract.

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

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

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

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

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

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

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

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

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

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

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

our recommendation that the autopsy be performed by a qualified neuropathologist to a qualified pathologist.

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

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

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

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

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

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

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

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

(Comment 81) Several comments supported our proposal to recommend that the requirements for infectious disease testing be applied to HCT/Ps designated for autologous use. Two comments expressed concern that the

recommendations in proposed § 1271.90(a) pertaining to reproductive tissue would have the same effect as requirements.

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

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

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

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

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

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

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

After reviewing these comments, we also realized that cryopreserved reproductive cells or tissue for autologous use or for use by a sexually intimate

partner, originally exempted from the donor screening and testing requirements, could be subsequently used for directed donation. Therefore, we have added an exception to the rule to accommodate individuals whose reproductive options have been restricted due to health or infertility. These individuals may not have undergone testing at the time of donation, because their intention at that time was autologous use or use in a sexually intimate partner. For various reasons, the donor(s) cannot make additional donations (e.g., the woman is post-menopausal or has her ovaries and uterus removed; the man has undergone chemotherapy, which renders him infertile.) To permit use of such cryopreserved cells or tissue for directed donation in situations where subsequent screening and testing is available, we have added § 1271.90(a)(3).

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

An example is the situation in which a sexually intimate couple create embryos, some of which are cryopreserved. The donors were not screened and tested at the time of the donation. The woman subsequently has her ovaries and uterus surgically removed, due to cancer. The donor couple wishes to

make a directed donation of the cryopreserved embryos to a recipient who is known to one or both of the donors prior to the donation. Under § 1271.90(a)(3), the embryos would be eligible for directed donation provided the couple can now be screened and tested.

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

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

E. Economic Impacts

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Comment 96) Three comments objected to our estimate of the cost of screening and testing oocyte donors and suggested that the actual cost is much higher.

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

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

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

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

(Response) We do not agree. The comment assumes the cost of an IVF cycle is \$10,000, whereas we assume the average cost of an ART cycle is \$11,868, a more general and somewhat larger number. Furthermore, the comment presents a net average revenue estimate for ART facilities, after

subtracting drug costs and oocyte retrieval fees. In the proposed rule, we present a gross average revenue estimate. It is therefore unclear that these estimates of average revenue can be meaningfully compared.

IV. Analysis of Economic Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Unfunded Mandates Reform Act requires that agencies prepare a written statement under section 202(a) of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation) in any one year. The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant economic impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact.

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action as defined by the Executive order, and so, is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure

in any one year of \$100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

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

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

A. Objectives and Basis of the Proposed Action

FDA is publishing this final rule as the next step in establishing regulations for the rapidly evolving HCT/P industry. This final rule is needed

to prevent unwitting use of contaminated tissues with the potential for transmitting infectious diseases, including HIV and hepatitis.

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

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

This final rule provides oversight for the full spectrum of HCT/Ps that are now marketed and may be marketed in the future. This action will improve

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

B. The Type and Number of Entities Affected

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

Information obtained under the registration final rule forms the basis for FDA's estimates of the number of affected eye banks and conventional tissue banks. The agency has not yet received all registration and listing information from reproductive tissue and hematopoietic stem/progenitor cells establishments, because registration and listing requirements for such establishments and products have not yet gone into effect. The agency's

estimates of the number of affected eye banks, hematopoietic stem/progenitor cell facilities, semen banks and ART facilities rely heavily on information obtained from various professional organizations associated with the HCT/P industry. Where good statistical data are not available, FDA's estimates have incorporated the quantitative judgments of individual experts identified through contacts with HCT/P industry professional associations.

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

Facilities that produce hematopoietic stem/progenitor cell products from peripheral blood or umbilical cord blood will also be affected by this final rule. FDA finds that available data with which to estimate the number of peripheral blood stem/progenitor cell (PBSC) facilities and evaluate current practices are quite limited, and the actual number of PBSC facilities may range from 200 to 400. As of April 2002, CBER has a record of 178 voluntarily registered facilities listing "stem cell" as a type of product or establishment. The National Marrow Donor Program (NMDP), which includes establishments that recover PBSCs, lists approximately 92 donor centers and 113 collection centers. Approximately 150 facilities involved with PBSC production are currently accredited by AABB and an estimated 107 are accredited by the

Foundation FACT. Industry sources estimate that approximately 80 of these facilities have or are seeking dual AABB/FACT accreditation, suggesting an unduplicated count of approximately 200 PBSC facilities assumed to be accredited by the AABB and/or FACT. However, the number and donor screening and testing practices of nonaccredited facilities are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of blood or bone marrow facilities may be as high as 400 (e.g., 200 more than the number estimated to be accredited by AABB and/or FACT), but the number of IBMTR/ABMTR-estimated facilities that actually process peripheral blood (as opposed to bone marrow) is uncertain. For the purposes of this analysis, FDA has assumed that 400 peripheral blood stem/progenitor cell facilities will be affected by this final rule.

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

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

Finally, this final rule also applies to facilities involved with reproductive tissue, primarily semen banks and ART facilities that collect and process donor

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

C. Nature of the Impact

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

This final rule also requires recordkeeping for donor-eligibility determinations. Manufacturers must ship HCT/Ps accompanied by documentation of donor eligibility status, including a summary of records that

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

The economic impact of these requirements is expected to be minor because the leading industry associations have already established standards for screening, testing and recordkeeping that, in most cases, meet or exceed the criteria specified in this final rule, and because existing FDA regulations already apply to certain HCT/Ps intended for transplantation (see part 1270). Table 1 of this document lists the types of HCT/Ps that will be affected by this final rule and the associated establishments that manufacture these products. Table 1 also provides estimates of the number of establishments affected by this final rule and the estimated percentage of establishments believed to be following current industry standards for donor screening and testing. The lists of specific donor screening and testing requirements proposed by FDA can be compared with those currently required by the industry associations.

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

Type of Human Tissue	Type of Entities Affected (and Estimated Total Number)	FDA Regulatory Requirements Compared to Industry Standards		Estimated Percent of Entities in Compliance With Industry Standards
		FDA	Industry Standards	
Nonreproductive Tissue				
Eye tissue	134 FDA registered eye tissue facilities, including 93 EBAA accredited eye banks (134 total)	21 CFR part 1270 and (s1,s2,s3) ¹ and (t1, t2, t3, t5) ²	EBAA (s1 through s3) ¹ and (t1 through t3) ²	100%
Pericardium, dura-mater, heart valves, skin allograft, bone allograft, other viable	166 FDA registered tissue banks, including 75 AATB accredited tissue banks (166 total)	21 CFR part 1270 and (s1 through s3) ¹ and (t1, t2, t3, t5) ²	AATB (s1 through s3) ¹ and (t1 through t5) ²	100%

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

Type of Human Tissue	Type of Entities Affected (and Estimated Total Number)	FDA Regulatory Requirements Compared to Industry Standards		Estimated Percent of Entities in Compliance With Industry Standards
		FDA	Industry Standards	
Stem progenitor cells; peripheral blood	178 FDA registered facilities, 92 NMDP donor centers, and 113 NMDP collection centers (400 total)	(s1 through s3) ¹ and (t1 through t6) ²	AABB/FACT (s1 through s3) ¹ and (t1 through t6) ²	100%
Stem progenitor cells; umbilical cord blood	Cord blood banks (25 total)	(s1 through s3) ¹ and (t1 through t6) ²	AABB/FACT (s1 through s3) ¹ and (t1 through t6) ²	100%
Licensed biological products and approved medical devices	67 FDA registered establishments (67 total)	Currently regulated under sections 351 and 361 of the PHS Act, 21 CFR parts 207 and 807		100% compliance with 21 CFR parts 207 and 807
Total	792 Facilities			
Reproductive Tissue				
Donor oocytes, embryos	370 ART facilities and associate labs in the 1999 SART report (400 total)	(s1 through s3) ¹ and (t1, t2, t3, t5) ²	ASRM/CAP (s1) ¹ and (t1,t2,t3,t5) ²	Unknown
Donor semen	4 Semen banks in 1996 AATB survey (110 total)	(s1 through s3) ¹ and (t1 through t8) ²	AATB (s1 through s3) ¹ and (t1 through t8) ² and ASRM (s1) ¹ and (t1, t2, t3, t5, t7, t8) ²	Unknown
Total	510 Facilities			

¹ Screening for: s1: HIV, s2: hepatitis, s3: CJD

² Laboratory Tests: t1: anti-HIV-1-2, t2: anti-HCV, t3: HBsAg, t4: anti-HTLV-I, t5: syphilis, t6: CMV, t7: *Neisseria gonorrhoea*, t8: *Chlamydia trachomatis*

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

In addition to the required donor screening and testing, this final rule will require facility staff time to align current quarantine, labeling, and recordkeeping systems with the new requirements. As shown in table 2 of this document, all of the industry associations already specify requirements for

these procedures. With the exception of facilities handling reproductive tissue, the current industry standards adopted by most facilities are at least as stringent as those included in this final rule.

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

FDA	AATB	EBAA	AABB	FACT	ASRM
Quarantine	X1	X1	X1	X1	X1
Labeling	X1	X1	X1	X1	X1
Record Retention	X1	X1	X1	X1	Recommended; not required

¹ X means corresponds.

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

1. Impact on Nonreproductive Tissue Establishments

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

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

In the proposed rule, FDA estimated that it would take approximately 8 to 40 hours to compare the new regulations against a facility's current SOPs

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

2. Impact on Reproductive Tissue Establishments

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

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

however, may entail further blood testing and adding some additional screening questions to the interview.

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

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

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

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

¹ \$275.40 x 4,559 = \$1,255,549

² \$275.40 x 9,118 = \$2,511,097

FDA believes that much of the additional screening and testing identified in table 3 of this document is already being performed by ART clinics.

Therefore, these estimates should be viewed as maximum expected cost burdens. Furthermore, certain methods of donor oocyte recovery, e.g., laparoscopy, are not directly connected with the transmission of sexually transmitted and genitourinary diseases and, therefore, testing for *Neisseria gonorrhoea* and *Chlamydia trachomatis* would not be required under this final rule. Use of such methods would be expected to lower the estimated testing costs by approximately \$40 per oocyte donor.

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

Based on conversations with semen banking industry experts, FDA estimates that the 20 largest semen banks account for approximately 95 percent of the commercial production of donor semen, and are following AATB

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

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

industry expert estimate of current U.S. TDI production of 100,000 units per year.

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

The screening cost per semen donor is assumed to include an initial medical history and physical, a 6-month followup exam, and an abbreviated screening at the time of each donation. Based on rates published on the Internet (Ref. 6), the agency estimates that a full medical exam costs \$175, a less extensive followup exam will cost approximately \$75 (a published fee for

a health history review), and the abbreviated screening at the time of each donation will cost approximately \$15 (i.e., one-fifth of the time required for a full history review). One repeat donor visit per year is assumed. Thus, the total cost of this screening is estimated to be \$265 per year per donor.

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

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

In the proposed rule, FDA estimated that the one-time review and alignment of current facility SOPs will require approximately 8 to 40 hours at each facility. Since we received no comments from affected entities, we have retained this assumption. As with nonreproductive tissue facilities, this process would be performed by a regulatory affairs analyst, a supervisor, or

a manager of quality assurance. Assuming a labor cost of \$40 per hour (Ref. 23), this standards reconciliation effort would result in a one-time cost per facility ranging from \$320 to \$1,600. Applying this range of cost per facility to the 400 ART clinics and 110 semen banks yields a potential one-time cost for all reproductive tissue facilities that ranges from \$163,200 ($\$320 \times (400 + 110)$) to \$816,000 ($\$1,600 \times (400 + 110)$).

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

TABLE 4.—RANGE OF RECURRING COSTS FOR REPRODUCTIVE TISSUE

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

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

super script

total

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

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tissue facilities than assumed in this analysis, the overall cost of compliance with this final rule will also be lower than these estimates suggest.

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

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

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

TABLE 5.—SUMMARY TABLE OF DONOR ELIGIBILITY COST ANALYSIS AT 7 PERCENT INTEREST OVER 10 YEARS¹

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

¹ All figures in thousands of dollars.

TABLE 6.—SUMMARY TABLE OF DONOR ELIGIBILITY COST ANALYSIS AT 3 PERCENT INTEREST OVER 10 YEARS¹

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

¹ All figures in thousands of dollars.

D. Benefits of the Final Rule

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

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

threatening chronic diseases that can be transmitted through donor tissue: HBV and HCV.

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

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

HBV-infected mothers can transmit the disease to their infants. Forty-two percent of infants born to women with HBsAg positivity (adjusted for HBeAg status) are at risk of HBV infection, and an additional 30 percent of infants born to HBsAg positive mothers become infected between 1 and 5 years of age. Prospective studies of infected infants and young children indicate that 25 percent will die from primary hepatocellular carcinoma (PHC) or cirrhosis as adults. The lifetime medical cost per case of PHC and cirrhosis is estimated to be \$96,500 (Ref. 17). An analysis of the cost-effectiveness of prenatal

screening and testing of mothers, with vaccination for positive screens, estimates that such screening and intervention would prevent 69 percent of the chronic HBV infections acquired perinatally or later in life (Ref. 18). This rate of effectiveness may provide an indication of the potential benefit of HBV screening required by this final rule.

The risk of transmission is estimated to be lower for HCV, compared to HBV. The CDC estimates the rate of sexual transmission between female to male partners, and the rate of transmission from mother to child, to each be approximately 5 percent. However, there is no vaccine intervention available for HCV, although interferon-alpha therapy has been found effective in eliminating the virus for at least some patients, and drug combinations (e.g., Interferon and Ribavirin) have been found to be even more effective. Although most patients infected with HCV are relatively healthy during most of their lives, an estimated 30 percent of those infected will eventually die of liver-related causes; an estimated 8,000 patients per year (Ref. 17). The average cost of care per year for persons with liver disease from chronic HCV is estimated to range from \$24,600 for patients without interferon-alpha therapy to \$26,500 per year for those receiving a 12-month course of therapy. The latter is estimated to provide patients with an additional 0.37 quality-adjusted life-years (QALYs) (Ref. 18).

Screening reproductive tissue donors is expected to significantly reduce the excess morbidity and mortality associated with HBV and HCV. As noted previously in this document, there are an estimated 4,559 to 9,118 oocyte donors and 2,565 semen donors per year. If these populations experience recently reported prevalence rates for HCV (1.8 percent) and HBV (4.9 percent) (Refs. 13 and 14), then screening for significant risk factors and disease markers

will result in reduced HBV and HCV exposures for the patient population at risk. The population at risk each year is estimated to include 3,022 to 9,066 women undergoing IVF with donor eggs, and 2,285 newborns delivered as a result of this therapy¹; and 34,200 to 70,000 women receiving TDI, and 8,800 newborns delivered as a result of that therapy.

E. Small Entity Impacts and Analysis of Alternatives

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

A 1995 study of conventional tissue banks (Ref. 20) reports average annual revenues of \$1.23 million per facility, which translates into \$1.45 million per facility (in 2002 dollars) based on inflation data reported by the Bureau of Labor Statistics. Most nonreproductive tissue facilities are assumed to have a comparable level of average revenues. Reproductive tissue industry experts estimate that 65 percent of ART facilities have average revenues of approximately \$2.5 million per year and the remaining 35 percent have average revenues of \$11.5 million per year. Industry experts also estimate that 19 of the 20 largest semen banks have average annual revenues of approximately

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

\$2 million per year, and 1 of the 20 largest facilities has annual revenues greater than \$8.5 million. Thus, the vast majority of facilities in each HCT/P industry sector are small entities. Nevertheless, as noted in the preceding cost analysis, most of these facilities will not be significantly impacted by this final rule because they are already meeting the infectious disease screening and testing and recordkeeping requirements.

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

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

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

As noted in table 7 of this document, the greatest expected cost will be incurred by facilities involved with reproductive tissue. Nevertheless, the estimated impact on most small facilities does not appear to be significant. The expected cost burden per facility ranges up to 0.35 percent of average

annual revenues. However, if current practices actually involve a much lower level of infectious disease screening and testing than assumed in this analysis, the impact of the new requirements would be greater than expected.

Although this final rule will impose some costs on small entities involved in the manufacture of HCT/Ps, the agency believes that this approach represents an effective means of protecting patient safety and public health. The less burdensome alternatives to this final rule involve fewer requirements for small entities (the vast majority of facilities in the HCT/P industry), but fail to provide fundamental assurances of product safety. For example, reliance on published FDA guidance for donor eligibility determination, rather than establishing a regulatory requirement, would provide the agency with no basis for ensuring compliance. Thus, agency guidance may have no greater influence than current voluntary industry standards, which have similar provisions, but have failed to persuade all facilities to adopt comprehensive screening and testing practices. FDA's guidance, alone, therefore, would not be expected to provide adequate protection from the public health risks associated with infected donor-derived HCT/Ps.

Another alternative would involve waiving some of the donor screening and testing requirements for small facilities. However, as noted previously, the vast majority of facilities in this industry are small. Moreover, this alternative would increase the safety risks associated with HCT/Ps if small facilities that currently screen and test donors on a voluntary basis choose to discontinue this practice due to an FDA-granted waiver. For example, waiving a requirement for donor screening would eliminate an extremely cost-effective first-tier level of safety protection because prospective donors deferred or disqualified at this stage need not undergo further testing. Similarly, waiving

the requirements for blood testing would expose patients, as well as tissue facility medical staff, to avoidable risks of infectious disease that may be undocumented in a patient's medical history, or be unknown to, or not mentioned by the living donor or cadaveric donor's family during screening.

We also considered waiving the requirement for semen quarantine and anonymous donor retesting to detect infections during the window period, when a donor's infection may not yet be detectable by blood tests. However, this alternative would expose recipients and the public to risks from infectious disease agents that cannot be immediately detected after exposure through most currently available blood tests (e.g., tests for HIV and HCV).

Recordkeeping for donor screening and testing is also critical to protecting product recipient and public safety. Adequate documentation and record retention ensure that HCT/Ps can be tracked to their source in the event of infection or other adverse reactions that result from donor tissue characteristics.

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

To help alleviate the impact on small entities while still protecting public health, the agency is not requiring that manufacturers follow screening and testing procedures when an HCT/P is used in the same person from whom

it is obtained, or in a sexually intimate partner of a reproductive tissue donor. The agency believes the risk of disease transmission from such activities is minimal. Further, in the case of reproductive HCT/Ps, the 6-month quarantine requirement applies only to semen from anonymous donors and not to oocytes and embryos.

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

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

V. Environmental Impact

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

VI. Federalism Assessment

Executive Order 13132, dated August 4, 1999, establishes the procedure that Federal agencies must follow when formulating and implementing policies that have federalism implications. The Executive order described nine

fundamental federalism principles, stressing the importance and sovereignty of State and local governments, and the contributions of individual States and communities to the development of enlightened public policy. Principles of federalism are inherent in the very structure of the Constitution and formalized in and protected by the Tenth Amendment. Regulations have federalism implications whenever they have a substantial direct effect on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Whenever a regulation has this result, the agency must prepare a federalism assessment.

The Executive order directs Federal agencies to:

1. Encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States;
2. Where possible, defer to the States to establish standards;
3. In determining whether to establish uniform national standards, consult with appropriate State and local officials as to the need for national standards and any alternatives that would limit the scope of national standards or otherwise preserve State prerogatives and authority; and
4. Where national standards are required by Federal statutes, consult with appropriate State and local officials in developing those standards.

This final rule establishes donor-eligibility and other related requirements for HCT/P establishments. In issuing this rule, we rely on the authority of section 361 of the PHS Act (42 U.S.C. 264), under which we may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (We also rely on our authority to issue CGMP regulations to

amend the existing CGMP regulations for drugs in 21 CFR parts 210 and 211, which include CGMP requirements, to incorporate the testing and screening provisions of part 1271 subpart C for HCT/Ps regulated as drugs, and/or biological products (see e.g., 21 U.S.C. 351(a)(2)(B)).

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

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

We received only one comment from a State official. This comment addressed abbreviated screening, which is discussed in comment 50 of this

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

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

However, we acknowledge that this final rule will have an effect in those areas where there has been no uniform Federal regulation. For example, this rule sets out testing and screening requirements for donors of reproductive cells and tissue, an area where there is a range of State regulation. Some of the State statutes and regulations that have come to our attention focus on the

risk of HIV transmission through semen donation and are thus more limited in their requirements than this final rule, which requires testing and screening for additional communicable disease agents and diseases and does not apply only to semen (see e.g., Ind. Code 16–41–14–7; Md. Code Ann., Health-Gen. 18–334(e); 12 Va. Admin. Code 5–90–240, 5–90–250).

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

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

In the proposed rule, we identified a particular area where we believed concerns about Federal preemption of State laws could arise: Legislative consent, or the recovery of corneas in accordance with State laws that allow the medical examiner or coroner to procure corneal tissue without the consent of the donor’s next of kin (64 FR 52696 at 52703). The proposed rule did not

contain an exception from the donor medical history interview for corneas procured under legislative consent. We recognized that, when corneal tissue is procured without the consent of the donor's next of kin, a donor medical history interview with the donor's next of kin does not necessarily occur. We noted, however, that the proposed definition of donor medical history interview would permit the interview to be conducted with an individual knowledgeable about the donor's medical history and relevant social behavior and would not require an interview with the next of kin. For that reason, we considered that the proposed rule and State laws on legislative consent may coexist, and we stated that we did not intend at that time to preempt those laws. We requested that affected parties submit specific, detailed comments on any potential conflicts that might make it impossible to comply with both this regulation and State laws on legislative consent.

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

Although we believe the final rule provides sufficient flexibility to allow for the continued recovery of corneas under legislative consent, we recognize that there may be some difficulty in communicating with the primary treating physician without obtaining permission from the deceased and/or the family

of the deceased, and that, therefore, this final rule may have a negative effect on the ability of medical examiners and coroners to recover corneas under State legislative consent laws. However, given the potential for corneas to transmit communicable disease, including TSE, we have concluded that making an exception from the requirement for a donor medical history interview in the case of corneas obtained under legislative consent is not justified.

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

VII. The Paperwork Reduction Act of 1995

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

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

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

Records used in determining the eligibility of a donor, i.e., results and interpretations of screening and testing, the donor eligibility determination, the name and address of the testing laboratory or laboratories, and the name of the responsible person who made the determination and the date, must be maintained (§ 1271.55(d)(1)). If any information on the donor is not in English, the HCT/P establishment must retain the original record and the statement of authenticity from the translator (§ 1271.55(d)(2)). HCT/P establishments must

retain the records pertaining to HCT/Ps at least 10 years after the date of administration, distribution, disposition, or expiration, whichever is latest (§ 1271.55(d)(4)).

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

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

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

Description of Respondents: HCT/P establishments.

As required by section 3506(c)(2)(B) of the PRA, we provided an opportunity for public comment on the information collection requirements

of the proposed rule (64 FR at 52715). Under the PRA, OMB reserved approval of the information collection burden in the proposed rule stating that they will make an assessment in light of public comments received on the proposed rule. One comment on the information collection burden was submitted to the docket.

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

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

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

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

TABLE 8.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.3(n)	1,302	60	78,136	1.0	78,136.0

TABLE 8.—ESTIMATED ANNUAL REPORTING BURDEN¹—Continued

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

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

TABLE 9.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

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

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

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

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

Our burden estimates for the annual frequency per response and average hours per response are based on institutional experience with comparable reporting and recordkeeping provisions for biological products. These burden

estimates have not changed. Also, we are adding burden estimates for §§ 1271.3(n) and 1271.47.

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

Under § 1271.3(n), approximately 1,302 establishments (166 conventional tissue establishments, 134 eye tissue establishments, 425 peripheral and cord blood stem/progenitor cell establishments, 510 reproductive tissue establishments, and 67 manufacturers of products regulated under the act and section 351 of the PHS Act) are required to have a documented medical history interview about the donor's medical history and relevant social behavior as part of the donor's relevant medical records for each of the estimated 78,136 donors (approximately 20,000 conventional tissue donors, 47,796 eye tissue donors, 5,700 peripheral and cord blood stem/progenitor cell donors, and 4,640 reproductive cell and tissue donors). We estimate that the time to conduct the interview with the donor, if living, or with an individual able to provide the information sought in the interview, is 1 hour.

Under § 1271.55(a), 972,417 HCT/Ps (approximately 750,000 conventional tissues, 94,186 eye tissues, 6,031 hematopoietic stem/progenitor cells, and 122,200 reproductive cells and tissues) are distributed per year. The agency estimates that, for each HCT/P, 1,235 establishments (1,302–67 establishments

with approved applications) will expend approximately 0.5 hours to prepare the summary of records. Conventional and eye tissue establishment are currently required to provide a summary of records under § 1270.33(d), which § 1271.55 replaces.

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

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

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

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

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

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

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

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

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

establishments and that each establishment would expend approximately 2.0 hours to create such document.

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

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

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

VIII. References

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

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7. Margolis, H. S., P. J. Coleman, R. E. Brown, et al., “Prevention of Hepatitis B Virus Transmission by Immunization: An Economic Analysis of Current Recommendations,” *Journal of the American Medical Association*, vol. 274, no. 15, pp. 1201–1208, 1995.

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14. McQuillan, G. M., P. J. Coleman, D. Kruszon-Moran, et al., "Prevalence of Hepatitis B Virus Infection in the United States: The National Health and Nutrition Examination Surveys, 1976 Through 1994," *American Journal of Public Health*, vol. 89(1), pp. 14-8, 1999.
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List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

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

21 CFR Part 820

Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 1271

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

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

**PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN
MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS;
GENERAL**

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

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

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

§ 210.1 Status of current good manufacturing practice regulations.

* * * * *

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

adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

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

§ 210.2 Applicability of current good manufacturing practice regulations.

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

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

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

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

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

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

§211.1 Scope.

* * * * *

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

* * * * *

PART 820—QUALITY SYSTEM REGULATION

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

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

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

§ 820.1 Scope.

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

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

* * * * *

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

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

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

§ 1271.1 [Amended]

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

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

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

* * * * *

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

[insert figure]

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

(j) *Colloid* means:

(1) A protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or

(2) Blood components such as plasma and platelets.

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

(l) *Directed reproductive donor* means a donor of reproductive cells or tissue (including semen, oocytes, and embryos to which the donor contributed the spermatozoa or oocyte) to a specific recipient, and who knows and is known by the recipient before donation. The term directed reproductive donor does not include a sexually intimate partner under § 1271.90.

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

(n) *Donor medical history interview means* a documented dialog about the donor's medical history and relevant social behavior, including activities, behaviors, and descriptions considered to increase the donor's relevant communicable disease risk:

(1) With the donor, if the donor is living and able to participate in the interview, or

(2) If not, with an individual or individuals able to provide the information sought in the interview (e.g., the donor's next-of-kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, and/or the primary treating physician).

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

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

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

(r) *Relevant communicable disease agent or disease* means:

(1)(i) For all human cells and tissues, a communicable disease or disease agent listed as follows:

(A) Human immunodeficiency virus, types 1 and 2;

(B) Hepatitis B virus;

(C) Hepatitis C virus;

(D) Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease; and

(E) *Treponema pallidum*.

(ii) For viable, leukocyte-rich cells and tissues, a cell-associated disease agent or disease listed as follows:

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

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

(iii) For reproductive cells or tissues, a disease agent or disease of the genitourinary tract listed as follows:

(A) *Chlamydia trachomatis*; and

(B) *Neisseria gonorrhoea*.

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

(i) For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with it, such as medical personnel, because the disease agent or disease:

(A) Is potentially transmissible by an HCT/P and

(B) Either of the following applies:

(1) The disease agent or disease has sufficient incidence and/or prevalence to affect the potential donor population, or

(2) The disease agent or disease may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection;

(ii) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and

(iii) For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available.

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

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

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

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

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

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

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

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

Subpart C—Donor Eligibility

Sec.

1271.45 What requirements does this subpart contain?

1271.47 What procedures must I establish and maintain?

1271.50 How do I determine whether a donor is eligible?

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

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

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

1271.75 How do I screen a donor?

1271.80 What are the general requirements for donor testing?

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

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

Subpart C—Donor Eligibility

§ 1271.45 What requirements does this subpart contain?

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

(b) *Donor-eligibility determination required.* A donor-eligibility determination, based on donor screening and testing for relevant communicable disease agents and diseases, is required for all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90. In the case of an embryo or of cells derived from an embryo, a donor-eligibility determination is required for both the oocyte donor and the semen donor.

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(c) *Prohibition on use.* An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, except as provided under §§ 1271.60(d), 1271.65(b), and 1271.90 of this subpart.

(d) *Applicability of requirements.* If you are an establishment that performs any function described in this subpart, you must comply with the requirements contained in this subpart that are applicable to that function.

§ 1271.47 What procedures must I establish and maintain?

(a) *General.* You must establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility, and complying with all other requirements of this subpart. Establish and maintain means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis. You must design these procedures to ensure compliance with the requirements of this subpart.

(b) *Review and approval.* Before implementation, a responsible person must review and approve all procedures.

(c) *Availability.* Procedures must be readily available to the personnel in the area where the operations to which they relate are performed, or in a nearby area if such availability is impractical.

(d) *Departures from procedures.* You must record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of its occurrence. You must not make available for distribution any HCT/P from a donor whose eligibility is determined under such a departure unless a responsible person has determined that the departure does not increase the risks of communicable disease transmission through the use of the HCT/P.

(e) *Standard procedures.* You may adopt current standard procedures, such as those in a technical manual prepared by another organization, provided that you have verified that the procedures are consistent with and at least as stringent as the requirements of this part and appropriate for your operations.

§ 1271.50 How do I determine whether a donor is eligible?

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

(b) *Eligible donor.* A donor is eligible under these provisions only if:

(1) Donor screening in accordance with § 1271.75 indicates that the donor:

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

(ii) Is free from communicable disease risks associated with xenotransplantation; and

(2) The results of donor testing for relevant communicable disease agents in accordance with §§ 1271.80 and 1271.85 are negative or nonreactive, except as provided in § 1271.80(d)(1).

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

(a) *Accompanying records.* Once a donor-eligibility determination has been made, the following must accompany the HCT/P at all times:

(1) A distinct identification code affixed to the HCT/P container, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining

to the HCT/P and, except in the case of autologous or directed reproductive donations, does not include an individual's name, social security number, or medical record number;

(2) A statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and

(3) A summary of the records used to make the donor-eligibility determination.

(b) *Summary of records.* The summary of records required by ~~sub~~⁹ paragraph (a)(3) of this section must contain the following information:

(1) A statement that the communicable disease testing was performed by a laboratory:

(i) Certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or

(ii) That has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services in accordance with those provisions;

(2) A listing and interpretation of the results of all communicable disease tests performed;

(3) The name and address of the establishment that made the donor-eligibility determination; and

(4) In the case of an HCT/P from a donor who is ineligible based on screening and released under paragraph (b) of § 1271.65, a statement noting the reason(s) for the determination of ineligibility.

(c) *Deletion of personal information.* The accompanying records required by this section must not contain the donor's name or other personal information that might identify the donor.

(d) *Record retention requirements.*

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(1) You must maintain documentation of:

(i) Results and interpretation of all testing for relevant communicable disease agents in compliance with §§ 1271.80 and 1271.85, as well as the name and address of the testing laboratory or laboratories;

(ii) Results and interpretation of all donor screening for communicable diseases in compliance with § 1271.75; and

(iii) The donor-eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

(2) All records must be accurate, indelible, and legible. Information on the identity and relevant medical records of the donor, as defined in § 1271.3(s), must be in English or, if in another language, must be retained and translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.

(3) You must retain required records and make them available for authorized inspection by or upon request from FDA. Records that can be readily retrieved from another location by electronic means are considered “retained.”

(4) You must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P’s distribution, disposition, or expiration, whichever is latest.

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

(a) *Quarantine.* You must keep an HCT/P in quarantine, as defined in § 1271.3(q), until completion of the donor-eligibility determination required by

§ 1271.50. You must quarantine semen from anonymous donors until the retesting required under § 1271.85(d) is complete.

(b) *Identification of HCT/Ps in quarantine.* You must clearly identify as quarantined an HCT/P that is in quarantine pending completion of a donor-eligibility determination. The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution.

(c) *Shipping of HCT/Ps in quarantine.* If you ship an HCT/P before completion of the donor-eligibility determination, you must keep it in quarantine during shipment. The HCT/P must be accompanied by records:

- (1) Identifying the donor (e.g., by a distinct identification code affixed to the HCT/P container);
- (2) Stating that the donor-eligibility determination has not been completed; and
- (3) Stating that the product must not be implanted, transplanted, infused, or transferred until completion of the donor-eligibility determination, except under the terms of paragraph (d) of this section.

(d) *Use in cases of urgent medical need.*

(1) This subpart C does not prohibit the implantation, transplantation, infusion, or transfer of an HCT/P from a donor for whom the donor-eligibility determination is not complete if there is a documented urgent medical need for the HCT/P, as defined in § 1271.3(u).

(2) If you make an HCT/P available for use under the provisions of paragraph (d)(1) of this section, you must prominently label it “NOT EVALUATED FOR INFECTIOUS SUBSTANCES,” and “WARNING: Advise patient of communicable disease risks.” The following information must accompany the HCT/P:

(i) The results of any donor screening required under § 1271.75 that has been completed;

(ii) The results of any testing required under § 1271.80 or 1271.85 that has been completed; and

(iii) A list of any screening or testing required under § 1271.75, 1271.80 or 1271.85 that has not yet been completed.

(3) If you are the establishment that manufactured an HCT/P used under the provisions of paragraph (d)(1) of this section, you must document that you notified the physician using the HCT/P that the testing and screening were not complete.

(4) In the case of an HCT/P used for an urgent medical need under the provisions of paragraph (d)(1) of this section, you must complete the donor-eligibility determination during or after the use of the HCT/P, and you must inform the physician of the results of the determination.

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

(a) *Storage.* If you are the establishment that stores the HCT/P, you must store or identify HCT/Ps from donors who have been determined to be ineligible in a physically separate area clearly identified for such use, or follow other procedures, such as automated designation, that are adequate to prevent improper release until destruction or other disposition of the HCT/P in accordance with paragraph (b) or (c) of this section.

(b) *Limited uses of HCT/P from ineligible donor.*

(1) An HCT/P from a donor who has been determined to be ineligible, based on the results of required testing and/or screening, is not prohibited by subpart C of this part from use for implantation, transplantation, infusion, or transfer under the following circumstances:

(i) The HCT/P is for allogeneic use in a first-degree or second-degree blood relative;

(ii) The HCT/P consists of reproductive cells or tissue from a directed reproductive donor, as defined in § 1271.3(l); or

(iii) There is a documented urgent medical need as defined in § 1271.3(u).

(2) You must prominently label an HCT/P made available for use under the provisions of paragraph (b)(1) of this section with the Biohazard legend shown in § 1271.3(h) with the statement “WARNING: Advise patient of communicable disease risks,” and, in the case of reactive test results, “WARNING: Reactive test results for (name of disease agent or disease).” The HCT/P must be accompanied by the records required under § 1271.55.

(3) If you are the establishment that manufactured an HCT/P used under the provisions of paragraph (b)(1) of this section, you must document that you notified the physician using the HCT/P of the results of testing and screening.

(c) *Nonclinical use.* You may make available for nonclinical purposes an HCT/P from a donor who has been determined to be ineligible, based on the results of required testing and/or screening, provided that it is labeled:

(1) “For Nonclinical Use Only” and

(2) With the Biohazard legend shown in § 1271.3(h).

§ 1271.75 How do I screen a donor?

(a) *All donors.* Except as provided under § 1271.90, if you are the establishment that performs donor screening, you must screen a donor of cells or tissue by reviewing the donor’s relevant medical records for:

(1) Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, including:

(i) Human immunodeficiency virus;

(ii) Hepatitis B virus;

(iii) Hepatitis C virus;

(iv) Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease;

(v) *Treponema pallidum*; and

(2) Communicable disease risks associated with xenotransplantation.

(b) *Donors of viable, leukocyte-rich cells or tissue.* In addition to the relevant communicable disease agents and diseases for which screening is required under paragraph (a) of this section, and except as provided under § 1271.90, you must screen the donor of viable, leukocyte-rich cells or tissue by reviewing the donor's relevant medical records for risk factors for and clinical evidence of relevant cell-associated communicable disease agents and diseases, including Human T-lymphotropic virus.

(c) *Donors of reproductive cells or tissue.* In addition to the relevant communicable disease agents and diseases for which screening is required under paragraphs (a) and (b) of this section, as applicable, and except as provided under § 1271.90, you must screen the donor of reproductive cells or tissue by reviewing the donor's relevant medical records for risk factors for and clinical evidence of infection due to relevant communicable diseases of the genitourinary tract. Such screening must include screening for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section. However, if the reproductive cells or tissues are recovered by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then screening for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section is not required. Communicable disease agents of the genitourinary tract for which you must screen include:

(1) *Chlamydia trachomatis*; and

(2) *Neisseria gonorrhoea*.

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

(1) A risk factor for or clinical evidence of any of the relevant communicable disease agents or diseases for which screening is required under paragraphs (a)(1)(i), (b), or (c) of this section; or

(2) Any communicable disease risk associated with xenotransplantation.

(e) *Abbreviated procedure for repeat donors*. If you have performed a complete donor screening procedure on a living donor within the previous 6 months, you may use an abbreviated donor screening procedure on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior.

§ 1271.80 What are the general requirements for donor testing?

(a) *Testing for relevant communicable diseases is required*. To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, if you are the establishment that performs donor testing, you must test a donor specimen for evidence of infection due to communicable disease agents in accordance with paragraph (c) of this section. You must test for those communicable disease agents specified in § 1271.85. In the case of a donor 1 month of age or younger, you must test a specimen from the birth mother instead of a specimen from the donor.

(b) *Timing of specimen collection*. You must collect the donor specimen at the time of recovery of cells or tissue from the donor. However, if collection at the time of recovery is not feasible, then you may collect the donor specimen

up to 7 days before or after recovery or, for donors of peripheral blood stem/progenitor cells only, up to 30 days before recovery. In the case of a repeat semen donor from whom a specimen has already been collected and tested, and for whom retesting is required under § 1271.85(d), you are not required to collect a donor specimen at the time of each donation.

(c) *Tests.* You must test using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases; however, until such time as appropriate FDA-licensed, approved, or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhoea* are available, you must use FDA-licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population. You must use a test specifically labeled for cadaveric specimens instead of a more generally labeled test when applicable and when available. Required testing under this section must be performed by a laboratory that either is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.

(d) *Ineligible donors.* You must determine the following donors to be ineligible:

(1) A donor whose specimen tests reactive on a screening test for a communicable disease agent in accordance with § 1271.85, except for a donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test;

(2)(i) A donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected, unless:

(A) You test a specimen taken from the donor before transfusion or infusion and up to 7 days before recovery of cells or tissue; or

(B) You use an appropriate algorithm designed to evaluate volumes administered in the 48 hours before specimen collection, and the algorithm shows that plasma dilution sufficient to affect the results of communicable disease testing has not occurred.

(ii) Clinical situations in which you must suspect plasma dilution sufficient to affect the results of communicable disease testing include but are not limited to the following:

(A) Blood loss is known or suspected in a donor over 12 years of age, and the donor has received a transfusion or infusion of any of the following, alone or in combination:

(1) More than 2,000 milliliters (mL) of blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or

(2) More than 2,000 mL of crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.

(B) Regardless of the presence or absence of blood loss, the donor is 12 years of age or younger and has received a transfusion or infusion of any amount of any of the following, alone or in combination:

(1) Blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or

(2) Crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.

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

(a) *All donors.* To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, you must test a specimen from the donor of cells or tissue, whether viable or nonviable, for evidence of infection due to relevant communicable disease agents, including:

- (1) Human immunodeficiency virus, type 1;
- (2) Human immunodeficiency virus, type 2;
- (3) Hepatitis B virus;
- (4) Hepatitis C virus; and
- (5) *Treponema pallidum*.

(b) *Donors of viable, leukocyte-rich cells or tissue.* In addition to the relevant communicable disease agents for which testing is required under paragraph (a) of this section, and except as provided under § 1271.90,

(1) You must test a specimen from the donor of viable, leukocyte-rich cells or tissue to adequately and appropriately reduce the risk of transmission of relevant cell-associated communicable diseases, including:

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

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

(c) *Donors of reproductive cells or tissue.* In addition to the communicable disease agents for which testing is required under paragraphs (a) and (b) of

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

(1) *Chlamydia trachomatis*; and

(2) *Neisseria gonorrhoea*.

(d) *Retesting anonymous semen donors*. Except as provided under § 1271.90 and except for directed reproductive donors as defined in § 1271.3(l), at least 6 months after the date of donation of semen from anonymous donors, you must collect a new specimen from the donor and test it for evidence of infection due to the communicable disease agents for which testing is required under paragraphs (a), (b), and (c) of this section.

(e) *Dura mater*. For donors of dura mater, you must perform an adequate assessment designed to detect evidence of transmissible spongiform encephalopathy.

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

(a) *Donor-eligibility determination not required*. You are not required to make a donor-eligibility determination under § 1271.50 or to perform donor screening or testing under §§ 1271.75, 1271.80 and 1271.85 for:

(1) Cells and tissues for autologous use; or

(2) Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or

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

(i) Additional donations are unavailable, for example, due to the infertility or health of a donor of the cryopreserved reproductive cells or tissue; and

(ii) Appropriate measures are taken to screen and test the donor(s) before transfer to the recipient.

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

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

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

(3) With the Biohazard legend shown in § 1271.3(h), with the statement "WARNING: Advise patient of communicable disease risks," and, in the case of reactive test results, "WARNING: Reactive test results for (name of disease agent or disease)" if the results of any screening or testing performed indicate:

(i) The presence of relevant communicable disease agents and/or

(ii) Risk factors for or clinical evidence of relevant communicable disease agents or diseases.

Dated: March 10, 2004

Lester M. Crawford

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

Dated: MAR 10 2004

Tommy G. Thompson

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

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