Conclusion

This action affects only certain design features on Boeing Model 747–SP airplanes modified by International Aviation Services, Ltd. It is not a rule of general applicability and affects only the applicant who applied to the FAA for approval of these features on the airplane.

The substance of the special conditions for this airplane has been subjected to the notice and comment procedure in several prior instances and has been derived without substantive change from those previously issued. It is unlikely that prior public comment would result in a significant change from the substance contained herein. For this reason, and because a delay would significantly affect the certification of the airplane, which is imminent, the FAA has determined that prior public notice and comment are unnecessary and impracticable, and good cause exists for adopting these special conditions immediately. Therefore, these special conditions are being made effective upon issuance. The FAA is requesting comments to allow interested persons to submit views that may not have been submitted in response to the prior opportunities for comment described above.

List of Subjects in 14 CFR Part 25

Aircraft, Aviation safety, Reporting and recordkeeping requirements.

The authority citation for these special conditions is as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701, 44702, 44704.

The Special Conditions

Accordingly, pursuant to the authority delegated to me by the Administrator, the following special conditions are issued as part of the type certification basis for Boeing Model 747–SP airplanes modified by International Aviation Services, Ltd.

1. *Protection from Unwanted Effects of High-Intensity Radiated Fields (HIRF).* Each electrical and electronic system that performs critical functions must be designed and installed to ensure that the operation and operational capability of these systems to perform critical functions are not adversely affected when the airplane is exposed to high intensity radiated fields.

For the purpose of these special conditions, the following definition applies:

Critical Functions. Functions whose failure would contribute to or cause a failure condition that would prevent the continued safe flight and landing of the airplane.

Issued in Renton, Washington, on July 17, 1997.

Gary L. Killion,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 97–19858 Filed 7–28–97; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16 and 1270

[Docket No. 93N–0453]

RIN 0910–AA40

Human Tissue Intended for Transplantation

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to require certain infectious disease testing, donor screening, and recordkeeping to help prevent the transmission of the human immunodeficiency virus (HIV), and hepatitis viruses through human tissue used in transplantation. In response to comments received, FDA has clarified and modified many of the provisions of the interim rule on human tissue intended for transplantation which was published in the **Federal Register** of December 14, 1993. The final rule requires facilities engaged in the recovery, screening, testing, processing, storing, or distributing of human tissues to ensure that specified minimum required medical screening and infectious disease testing has been performed and that records documenting such screening and testing for each human tissue are available for inspection by FDA. The regulations also contain provisions for the inspection of such facilities and for retaining, recalling, or destroying human tissue for which appropriate documentation is not available.

DATES: The regulation is effective January 26, 1998. This effective date is applicable to all human tissue intended for transplantation procured on or after this date. Written comments on the information collection requirements should be submitted by September 29, 1997.

ADDRESSES: Submit written comments on the information collection requirements to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Background

In the **Federal Register** of December 14, 1993 (58 FR 65514), FDA issued an interim rule on human tissue intended for transplantation (hereinafter referred to as the interim rule). These regulations became effective upon the date of publication in the **Federal Register** and required human tissue in storage as of that date to be in compliance. The interim rule was issued because of evidence indicating an immediate need to protect the public health from the transmission of HIV infection and hepatitis infection through transplantation of human tissue from known donors infected with or at risk for these diseases. The movement towards regulating human tissue was accelerated by a hearing on appropriate oversight for human tissue banking chaired by Senator (then Representative) Wyden before the Subcommittee on Regulation, Business Opportunities and Technology of the Committee on Small Business held on October 15, 1993. At the hearing, representatives of persons involved in human tissue banking advocated that legislation setting forth regulatory requirements for human tissue banking be passed. There was testimony that human tissues from foreign sources were being offered for sale in the United States with little documentation as to the source of the human tissue, the cause of death, the medical conditions of the donor, or the results of donor screening and testing. This raised significant concerns about the safety and quality of some of the human tissue available for transplantation. As a result of a number of similar allegations, the agency initiated inquiries into the possibility that human tissues intended for transplantation were being supplied without appropriate infectious disease testing and medical screening. In a relatively brief period of time, the agency was able to confirm the availability for importation and distribution to the United States of

human tissue that did not follow adequate screening and testing standards to prevent transmission of infectious disease.

In the early 1990's, prior to the above-mentioned reports of the distribution of imported human tissue not following adequate screening and testing standards, the Centers for Disease Control and Prevention (CDC) reported that HIV had been transmitted through transplantation of human tissue. Based in part on the CDC report, the Assistant Secretary for Health convened a Public Health Service Work Group to evaluate the need for and type of Federal oversight that should be developed for human tissue. In its report on July 18, 1991, the Work Group recommended Federal development and publication of standards or guidance on donor screening, testing, recordkeeping and tracking procedures to reduce the risk of transmission of infectious disease. The Work Group recommended that Federal agencies, including FDA, proceed with pending regulations as ''expeditiously as possible.'' The Work Group charged FDA to ''continue to assert its jurisdiction over tissues on a product-by-product basis to ensure adequate oversight.'' The Work Group noted that investigation into the needed level of mandatory oversight for human tissue transplantation, apart from organ and bone marrow transplantation, should take place and recommended that FDA evaluate this issue. Subsequently, FDA issued the interim rule.

Since the interim rule was issued, FDA has issued 15 orders for retention, recall, and destruction of violative human tissue. In March 1995, following receipt of an order for retention, recall, and destruction that caused shipments of a firm's processed allografts to be held, a processor of human tissue filed a complaint in Federal District Court challenging FDA's interim rule and the application of internal guidance on the interim rule issued to field investigators. The court issued the plaintiff preliminary injunctive relief by enjoining FDA from detaining particular shipments of the plaintiff's tissue. The plaintiff and FDA subsequently entered into an agreement settling their dispute, and the plaintiff's complaint was dismissed.

After FDA issued the interim rule, FDA held three separate workshops to promote continuous dialogue between FDA and the human tissue industry. The first workshop, which FDA announced in the **Federal Register** of June 10, 1994 (59 FR 29950), was entitled ''Public Workshop on Human Tissue Intended for Transplantation'' and was held on June 20, 1994 (hereinafter referred to as the June 1994 workshop). An objective of the workshop was to give industry the opportunity to discuss practical concerns relating to the implementation of the interim rule. It was the intention of FDA to review and consider the discussion of these topics in the development of any future rulemaking. The comment period on the interim rule closed March 14, 1994, but was reopened until August 20, 1994, to allow interested persons additional time to submit comments on both the interim rule and the workshop.

In the **Federal Register** of February 17, 1995 (60 FR 9335), FDA announced that the Blood Products Advisory Committee, scheduled to meet on March 23 and 24, 1995, would participate in a workshop entitled ''Human Tissue Intended for Transplantation and Human Reproductive Tissue: Donor Screening and Infectious Disease Testing'' (hereinafter referred to as the March 1995 workshop). The topics discussed at the workshop were: (1) Recommendations for donor screening and infectious disease testing for human tissue intended for transplantation, (2) draft discussion points for screening and testing donors of human reproductive tissue, and (3) a draft registration form. FDA made the ''Draft Discussion Points for Screening and Testing Donors of Human Tissue Intended for Transplantation and Human Reproductive Tissue,'' and the draft establishment registration form available before and at the meeting.

In the **Federal Register** of May 24, 1995 (60 FR 27406), FDA announced a third workshop on human tissue. This workshop, entitled ''Human Tissue for Transplantation and Human Reproductive Tissue: Scientific and Regulatory Issues and Perspectives'', was held on June 20 and 21, 1995 (hereinafter referred to as the June 1995 workshop). The purpose of this workshop was to provide an opportunity for continued discussion of the regulation of human tissue for transplantation. The workshop consisted of plenary and breakout sessions that focused on the following topics: (1) Donor screening, (2) infectious disease testing and inactivation methods, (3) voluntary standards, (4) assessment of industry practices related to tracking, (5) interactions with organ procurement organizations and procurement coordination practices, and (6) State regulatory approaches and industry practices. FDA offered a draft discussion document concerning the screening and testing of donors of human tissue intended for transplantation in advance and at the workshop. The availability of the draft document was announced in the **Federal Register** of June 20, 1995 (60 FR 32128). FDA requested that comments on the draft document be sent to the Dockets Management Branch by July 20, 1995, for consideration in the drafting of a guidance document.

In response to industry requests for clearer guidance on donor screening and in an effort to consolidate and disseminate recommendations on the screening of donors for signs and symptoms of infectious disease, FDA has prepared a document entitled ''Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation,'' the availability of which is announced elsewhere in this issue of the **Federal Register**. This guidance was prepared taking into account the issues addressed in the draft document distributed at the workshop and comments received.

The final rule takes into account comments submitted to the Dockets Management Branch, and discussions and information obtained through public participation in the three workshops. The agency is taking this action to provide clarification of the interim rule and to finalize its provisions.

B. Scientific and Legal Justification

The use of HIV antibody testing on donors of human tissue makes the human tissue inventory safer. However, it does not eliminate the ''window'' period between the time of infection and the presence of detectable levels of antibodies to HIV. Therefore, as an added safety measure FDA requires screening for behavioral and high risk information in addition to testing for infection with the virus so that the safest product will be made available. Like the HIV virus, evidence of hepatitis B and hepatitis C is determined by screening and testing human tissue donors. Since HIV and hepatitis viruses are transmitted by parenteral and sexual modes, exclusion of potentially infected donations by both screening and testing the human tissue donor has been found to be reliable and widely accepted. These viruses may be transmitted by a wide range of human tissue including solid organs, musculoskeletal and integumentary tissue, and body fluids (e.g., semen and breast milk).

FDA is issuing these regulatory requirements under the legal authority of section 361 of the Public Health Service Act (the PHS Act, 42 U.S.C. 264). This section authorizes the Secretary of the Department of Health and Human Services (the Secretary), to make and enforce such regulations as

judged necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or from State to State. Intrastate transactions may be regulated under authority of this provision, as appropriate (see *State of Louisiana* v. *Mathews*, 427 F. Supp. 174 (E. D. La. 1977)). Section 361 of the PHS Act also provides for such inspection and destruction of articles found to be so infected or contaminated as to be sources of dangerous infection to humans, and other measures, as may be deemed by the Secretary to be necessary. Section 361 of the PHS Act has been invoked by FDA to regulate various activities or articles. For example, FDA has invoked this authority to regulate conveyance sanitation, the source and use of potable water, and milk pasteurization. The agency has also acted under section 361 of the PHS Act to prevent the transmission of communicable disease through shellfish, turtles, certain birds, and bristle brushes (see 21 CFR parts 1240 and 1250). FDA has also relied in part on section 361 of the PHS Act in issuing requirements to protect the blood supply.

Authority for the enforcement of section 361 of the PHS Act is provided for in part under section 368 of the PHS Act (42 U.S.C. 271). Under section 368(a), any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year (42 U.S.C. 271(a)). Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted (18 U.S.C. 3559 and 3571(c)). In addition, Federal District Courts have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act.

II. Highlights of the Final Rule

The final rule provides clarification of certain provisions of the interim rule and responds to the comments and concerns expressed. In response to comments received on the interim rule, definitions have been added or modified for the following terms: Blood component, colloid, contract services, crystalloid, donor medical history interview, establishment, importer of record, legislative consent, person, physical assessment, plasma dilution, reconstituted blood, relevant medical records, responsible person, and summary of records. The final rule further elaborates on the requirements for: (1) Criteria for using an algorithm when determining plasma dilution, (2) documents to be included in the summary of records, (3) responsibility for maintaining the records used in determining the suitability of the tissue for transplantation, (4) the relevant medical records for corneal tissue recovered under legislative consent, and (5) the shipment of tissue. The rule also describes the steps to be followed when human tissue is offered for import.

Due to the renumbering of many of the sections in the rule the following chart is being provided for comparison:

TABLE 1.—COMPARISON CHART OF FINAL AND INTERIM RULES

Final Rule (section)	Interim Rule (section)	Nature of Change
Subpart A—General Provisions		
Scope 1270.1(a)(b)(c)(d)	1270.1(a)(b)	Additional exemptions added.
Definitions 1270.3(a)–(x)	1270.3(a)–(i)	Definitions added for: (b) blood component, (c) colloid, (d) contract services, (e) crystalloid, (h) donor medical history interview, (i) establishment, (k) importer of record, (l) legislative consent, (m) person, (n) physical assessment, (o) plasma dilution, (r) reconstituted blood, (t) relevant medical records, (u) responsible person, (w) summary of records.
1270.5 through 1270.20		Removed.
Subpart B—Donor Screening and Testing		
Human Tissue Intended for Transplantation 1270.21(a)–(h)	1270.5(a)–(f)	Renumbered. Clarification of (e) summary of records, addition of (b) testing of neonate donor (g) standards for corneal retrieval, and (h) plasma dilution.
Subpart C—Procedures and Records		
Written Procedures 1270.31(a)–(e)	1270.7(a)–(c)	Renumbered. Original paragraph (c) is now paragraph (e), new paragraphs (c) and (d) require written procedures for designating and identifying quarantined tissue and for preventing contamination or cross-contamination of tissue during processing.

TABLE 1.—COMPARISON CHART OF FINAL AND INTERIM RULES—Continued

Final Rule (section)	Interim Rule (section)	Nature of Change
Records, General Requirements 1270.33(a)–(h)	1270.9(a)–(e)	Renumbered. Paragraphs (c) and (d) contain requirements for shipment of human tissue prior to and after a determination of suitability for transplantation is made. Original paragraphs (c),(d), and (e) are now paragraphs(f),(g), and (h), respectively. Paragraph (f) is amended to clarify who is responsible for record retention.
Specific Records 1270.35(a)–(d)	1270.11(a)–(c)	Renumbered. Original paragraphs (b) and (c) are now paragraphs (d) and (b) respectively. New paragraph (c) was added to require documentation of receipt and distribution of human tissue.
Subpart D—Inspection of Tissue Establishments		
Inspection 1270.41(a)–(e)	1270.13(a)–(e)	Renumbered.
1270.42(a)–(b)	none	Added steps to be followed when human tissue is offered for import.
1270.43(a)–(e)	1270.15(a)–(e)	Renumbered.

III. Comments on the Interim Rule and FDA Responses

FDA received 73 comments on the interim rule. Many comments supported FDA's effort to prevent transmission of disease through transplantation and the positive effect the interim rule had on nationwide standardization. Other comments, primarily from representatives and supporters of eye banks, objected to the interim rule. The comments stated that implementation of the rule temporarily halted transplantation operations of human tissue and argued that the industry should be allowed to continue regulating itself because of its excellent record in preventing the transmission of disease.

In general, the comments requested clarification and modification of selected sections of the interim rule, presented data supporting the suggested changes, and described burdens that particular sections would impose, e.g., the effect on cornea recovery by the requirement for a next of kin interview in States or territories with medical examiner laws, the retrospective review of tissue in storage for compliance, cadaveric specimen testing, and the import/export of human tissue from countries without certified laboratories under the Clinical Laboratories Improvement Amendments of 1988 (CLIA).

A. General Comments

1. One comment stated that the public health was threatened by the interim rule in that it contributed to an existing backlog demand for processed human tissue.

FDA recognizes that there may have been some temporary shortages of a few types of human tissue due to a small amount of human tissue in storage not being in compliance with the interim rule, but is not aware of instances where the public health was affected adversely. FDA took voluntary industry standards and State requirements into account in issuing the rule to lessen the impact of the implementation of the interim rule.

2. One comment stated that organ transplantation should be included in the scope of the interim rule and inquired as to why it was not covered.

The National Organ Transplant Act of 1984 provides for Federal oversight of the human organ transplantation system. The Health Resources Services Administration (HRSA) within the Department of Health and Human Services (DHHS) currently administers programs related to human organ transplantation. Human organs are specifically excluded from the interim rule and the final rule (new § 1270.3(j)(4)) because they are already regulated under existing Federal oversight programs and FDA does not believe that additional oversight by FDA is needed at this time.

3. Twenty-six comments maintained that eye banks adhere to strict internal standards, have an excellent track record with few documented disease transmission cases, and should not be regulated by the government.

The agency acknowledges that the trade associations for eye banks, the American Association of Tissue Banks (AATB) and the Eye Banks Association of America (EBAA) are recognized to have strict internal standards and that the eye banks have a reputation for conscientious adherence to those standards. The agency notes, however, that although corneas may have a degree of protection due to avascularity, they can, like other tissues, carry viruses and transmit communicable diseases. Therefore, FDA believes that corneas should be subject to the same regulatory oversight as other tissues. The agency would also note that the regulation will impose little or no burden for eye banks that are in compliance with the voluntary AATB and EBAA standards because these standards are substantially similar to the requirements of the regulation.

4. Two comments supported required testing by CLIA-certified laboratories.

Under provisions of the 1988 Amendments to the Clinical Laboratories Improvement Act of 1967 (CLIA '88), laboratories engaged in testing specimens in interstate commerce must meet the requirements of section 353 of the Public Health Service Act (42 U.S.C. 263a) in order to be licensed or remain licensed for testing in interstate commerce. CLIA applies to laboratories, including physicians' office laboratories, that test human specimens. Under CLIA '88,

such laboratories are subject to regulations designed to ensure the quality and reliability of medical tests they perform. Therefore, the requirement that all infectious disease testing be performed by CLIA-certified laboratories, helps ensure standardized testing on all donors of human tissue intended for transplantation.

5. One comment inquired if contract processing is permitted under the interim rule.

FDA realizes that not all human tissue establishments have the facilities to perform all manufacturing steps. It may be more cost effective for establishments to contract out some testing and processing procedures. There is no prohibition in the interim rule or final rule concerning such contract services. Therefore, contract services have been added to the definitions in § 1270.3 (21 CFR 1270.3). FDA has revised § 1270.41(a) (21 CFR 1270.41(a)) to clarify that such contract services are subject to inspections conducted by authorized representatives of FDA.

6. Two comments urged the expedited publication of the draft guidance document *Draft USPHS Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs*, that provides specific questions for use in donor behavioral and high risk information screening.

At the time of publication of the interim rule, the final version of the guidance document had not been made available. The Public Health Service (PHS) published the final guideline on May 20, 1994, in the *Morbidity and Mortality Weekly Report* (MMWR 1994:43, 1–17). FDA considered these guidelines and previous PHS guidelines in the preparation of the final rule and the guidance document that is being announced as available by FDA elsewhere in this issue of the **Federal Register**. The guidance document provides recommendations on appropriate questions, clinical evidence, and physical evidence for use in donor screening.

7. Two comments were made on alternative methods of preventing transmission of HIV–1, HIV–2, hepatitis B, and hepatitis C viruses. One comment asked that the rule provide for a waiver process based on alternative methods of viral inactivation. One of the comments added that claims of processes that result in viral inactivation or sterility should be investigated for scientific accuracy prior to exemption from any portion of these rules.

Presently, FDA is unaware of any alternative method of viral inactivation that FDA believes warrants omission of HIV and hepatitis testing. Therefore, FDA does not believe that such a change is warranted at this time. FDA is interested in public comment on this issue and will consider whether to include in future rulemaking a process for the agency to grant waivers from any regulation under part 1270 (21 CFR part 1270).

8. Two comments recommended that an expert advisory committee, to include transplant surgeons as members, be established as soon as possible to review and make recommendations for future rulemaking.

Since the time the interim rule was published, FDA has requested the Blood Products Advisory Committee (BPAC) to review data and make recommendations regarding human tissue for transplantation in addition to blood products. The agency recognizes the positive contribution of experienced professionals in providing FDA with assistance on regulatory issues and believes that the BPAC can serve in an advisory role on human tissue intended for transplantation.

On July 13, 1995, a report by the Institute of Medicine (IOM) entitled ''HIV and the Blood Supply: An Analysis in Crisis Decisionmaking'' was released. The Secretary directed this investigation in response to concerns voiced by the hemophilia community concerning events leading to the transmission of HIV to individuals with hemophilia from contaminated blood products. FDA has made certain changes to BPAC consistent with recommendations in the report. In particular, FDA has reformulated the membership of BPAC to limit industry-affiliated representation to a single, nonvoting representative. Additionally, FDA has revised the BPAC charter to expand the possibility for consumer representation.

B. Comments on Specific Provisions in the Interim Rule

FDA has revised the interim rule as a result of comments submitted to the docket. In addition, FDA on its own initiative is making changes to clarify the requirements of the rule and its application to the tissue industry. The term ''banked'' has been deleted from the phrase ''banked human tissue intended for transplantation'' wherever it appears in the regulations because FDA believes the term ''banked'' is unnecessary with respect to human tissues covered by this final rule

1. Scope (§ 1270.1)

Section 1270.1 defines the scope of the regulations governing human tissue intended for transplantation to include human tissue and establishments or persons engaged in the recovery, processing, storage, or distribution of human tissue. FDA has revised § 1270.1 by explicitly stating that screening and testing activities are subject to regulation. The final rule also clarifies that at this time the regulations do not apply to human tissue intended for autologous use. FDA is, however, currently conducting a review of human tissues that includes autologous use and is considering proposing additional regulations in this area.

9. One comment asked that practitioners in transplant establishments who only store human tissue for transplant in their own facilities be relieved from compliance with the provisions of the rule.

FDA recognizes that there are instances where human tissue is received and stored temporarily in a hospital or other clinical facility pending scheduled surgery within the same facility. FDA agrees that hospitals or other clinical facilities that only receive and store human tissue for transplantation within the same facility should not be covered by the rule and thus FDA has added this provision in § 1270.1(d) of the final rule. Those hospitals or clinical facilities that participate in the recovery, screening, testing, processing, or distribution of human tissue in addition to storage for transplantation are covered by the rule.

2. Definitions (§ 1270.3)

Section 1270.3 defines various terms used in the regulations. In the final rule FDA has clarified, revised and simplified the definitions. For clarity, FDA has added the terms ''shipment,'' and ''exportation'' to the definition of ''distribution'' (§ 1270.3(f) of the final rule). The definition of ''processing'' (§ 1270.3(p) of the final rule) has been revised by deleting the word ''potency'' and by adding that processing includes ''the inactivation or removal of adventitious agents.'' The phrase ''human tissue that has not yet been characterized as suitable for transplantation'' has been added to clarify the definition of ''quarantine'' (§ 1270.3(q) of the final rule). The definition of ''storage'' (§ 1270.3(v) of the final rule) has been simplified by deleting any reference to the facility holding the tissue. The term ''native vasculature'' has been replaced by the term ''original blood vessels'' in the definition of ''vascularized'' (§ 1270.3(x) of the final rule).

10. One comment suggested that the rule apply to normal human cells such

as hepatocytes that can be transplanted with little or no manipulation.

The agency declines to accept the comment's suggestion. The rule covers human tissue such as bone, ligament, tendons, fascia, cartilage, corneas, and skin. Hepatocytes and other cellular based therapies are regulated by FDA as biological products. (See description in ''Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products'' (58 FR 53248).)

11. One comment asked for definition of the following terms: (1) Blood component, (2) colloid or volume expander, (3) crystalloid, (4) hemodilution, and (5) pretransfusion specimen.

FDA agrees that some additional definitions should be included and is amending § 1270.3 to include definitions for ''blood component,'' ''colloid'' (volume expander), ''contract services,'' ''crystalloid,'' ''donor medical history interview,'' ''establishment,'' ''importer of record,'' ''legislative consent,'' ''person,'' ''physical assessment,'' ''plasma dilution'' (to replace ''hemodilution''), ''relevant medical records,'' ''reconstituted blood,'' ''responsible person,'' and ''summary of records.'' FDA believes that the term ''pretransfusion specimen'' is self explanatory, therefore, a definition has not been added.

12. One comment requested that the definition of ''vascularized'' that appears in § 1270.3(c) of the interim rule be clarified.

FDA agrees that the definition of vascularized should be clarified and has revised the definition.

13. Two comments requested a revision to the definition of human tissue to specifically exclude human organs and those human tissues that have been chemically or biophysically altered, such as heart valves.

The definition of human tissue found in § 1270.3(b) of the interim rule (§ 1270.3(j) of the final rule) contains a specific exclusion for vascularized organs (kidney, liver, heart, lung, pancreas, or other vascularized human organs). Allograft heart valves, dura mater allografts, epikeratophakia lenticules, preserved umbilical cord vein grafts, and various skin and bone products that have been chemically or biophysically altered are currently regulated as devices under the authority of the Medical Device Amendments of 1976 (Pub. L. 94–295) and are therefore excluded from this definition of human tissue. However, FDA is considering the regulation under part 1270 of human heart valve allografts and certain other tissues now regulated as devices. To allow all interested persons to comment on this regulatory change, FDA intends to provide notice and request for comment on such regulation in the **Federal Register** at a future date. Human tissues that are processed in ways to only reduce infectivity or preserve human tissue integrity are regulated under part 1270.

3. Donor Testing (§ 1270.21)

Section 1270.5 of the interim rule specifies the requirements for testing donor blood specimens for evidence of communicable viruses, i.e., HIV–1, HIV–2, hepatitis B, and hepatitis C. It requires that these tests be done using FDA licensed test kits approved for such use by FDA and performed in a laboratory certified under CLIA. In the final rule, FDA has deleted the terms ''blood'' and ''serological'' and the name of the communicable virus has been listed in place of a specific marker test. This change has been made to allow for future advancement in science and technology which could cause a change in the appropriate test methodology. Section 1270.5(e) of the interim rule has been split into § 1270.21(f) and (g) of the final rule, in part to clarify the revised requirements for corneal tissue retrieval.

14. One comment inquired if human tissue would be considered suitable for transplantation if a repeatedly reactive screening test for any of the viral marker tests was negative by confirmatory testing. Some comments have encouraged FDA to allow the use of tissue for which blood specimens tested repeatedly reactive for hepatitis B surface antigen (HBsAg), if the results of confirmatory neutralization testing do not confirm the results of the screening.

FDA does not concur with this suggestion. With current tests, early HIV, hepatitis B virus, and hepatitis C virus infections can be missed by the respective confirmatory test due to differences in the sensitivity of the tests, albeit at a low frequency. The agency is clarifying in the final rule, that suitability of human tissue shall be determined by the results of screening tests for the required viral markers. The rule requires that the donor be free of evidence of HIV, hepatitis B, and hepatitis C. A repeatedly reactive screening test for any of the viral markers indicates that the donor may have been exposed to and infected with the particular virus. Any indication of the possibility of infection must be taken into consideration when determining the suitability of the human tissue. The use of screening tests in determining the suitability of the donor of human tissue intended for transplantation is clarified in § 1270.21(a) of the final rule which specifically identifies ''screening * * *'' as the required test. Therefore, tissue that is repeatedly reactive is not suitable for use even if confirmatory tests are negative. In addition, if the tissue establishment becomes aware of indeterminate, repeatedly reactive, or positive test results relative to HIV or hepatitis, even if the tests are not specifically required by the final rule, then the tissue is considered not suitable for transplantation.

15. Seven comments questioned the validity of certain viral marker tests using cadaveric blood specimens. Concern was expressed over the inadequate data that exists on the testing of cadaveric blood specimens using FDA licensed screening kits for viral markers and guidance was requested in determining the suitability of the donor.

FDA is aware of the need to clarify the appropriateness of using cadaveric specimens, i.e., a blood specimen taken from a donor whose heartbeat has ceased, with the currently licensed test kits. Generally, the concern is that test results based on testing of cadaveric blood specimens that exhibit some degree of hemolysis and/or lipemia may not be accurate. FDA is working with manufacturers towards validation of assays for cadaveric specimen use. Screening tests that have been approved for testing cadaveric blood are to be used, once FDA approval has been given and the labeling of the test kit has been modified to specifically indicate the use of cadaveric blood specimens.

16. One comment dealt with a letter issued by CBER on December 28, 1993, to the tissue industry (hereinafter referred to as the December 1993 letter). This letter, which was intended to provide clarification to the industry regarding HIV–2 testing, contained the statement, ''as long as the tissue was tested by the best available test methods at the time, and the newly available test methodology was adopted in a timely manner, the tissue continues to be suitable for transplant.'' The comment said this statement may be misleading because it could be interpreted to include other newly licensed tests in addition to tests for HIV–2.

Because the December 1993 letter addresses HIV–2 testing only, FDA does not believe the statement cited by the comment could be easily misinterpreted as referring to tests for other infectious agents.

17. Three comments requested further explanation of the approval requirements for laboratories doing screening tests on donor specimens. Specifically requested, was clarification

of the term ''registered and certified under CLIA'' and recognition, by the Health Care Finance Administration (HCFA), of accreditation by an acceptable alternative inspection organization.

Shortly after publication of the interim rule, FDA provided guidance regarding § 1270.5(b) in the December 1993 letter. Laboratories have the option of coming under the jurisdiction of HCFA directly, or indirectly by way of accreditation by a private accreditation organization approved by HCFA for ''deemed status,'' or by being located in a State approved for exemption under CLIA. In the December 1993 letter, FDA recognized that many laboratories had been registered but not yet certified under CLIA, because: (1) They had not yet been surveyed (inspected) by HCFA or one of its agents; (2) they had been surveyed but had not yet received their certificate of compliance; or (3) the accrediting organization performing the survey had applied for but had not yet received approval by HCFA for ''deemed status'' under the 1988 amendments. During this transition period, FDA stated that its preliminary interpretation was that a laboratory was suitable for performing the testing required by the interim rule provided: (1) The laboratory had an active and current history of being surveyed by HCFA or one of its agents, by a private accrediting organization, or an organization whose approval by HCFA was pending; (2) the laboratory was in good standing with HCFA, and if applicable, FDA, in that there was no regulatory action either pending or in effect that would limit the laboratory's ability to perform the types of tests that are required in the interim rule; and (3) the laboratory was registered with HCFA at that time. Since the publication of the interim rule, HCFA has completed the first survey of registered laboratories. All laboratories that have met the inspection criteria have been issued certification under CLIA. Thus, laboratories must now be certified under CLIA.

18. One comment on § 1270.5(a) (§ 1270.21(a) of the final rule) urged that tests such as those run on lymph node tissue or vitreous humor be considered in the absence of an appropriate blood specimen.

In § 1270.21 of the final rule, FDA has deleted the identification of blood as the source of specimen required for infectious disease testing, recognizing advances in technology and the possibility of future approval of viral marker testing (used in determining donor suitability) that may utilize alternative specimen sources. At this time, blood is the only specimen approved for use with FDA licensed viral marker tests to determine donor suitability.

19. One comment on § 1270.5(b) (§ 1270.21(c) of the final rule) asserted that the rule discriminates against importers of human tissue because they are unable to comply with the requirement for testing by a CLIA certified laboratory.

During a congressional hearing held on October 15, 1993, testimony was given with respect to an increase of unsuitable human tissue derived from foreign sources being offered for sale in the United States by individuals unwilling to declare the actual source of the human tissue, to provide documentation as to the cause of death, the medical records of the donor, the results of donor screening and testing, or to furnish specimens of donor serum for testing. Human tissue imported from outside the United States must meet the same standards of donor screening, testing, and tissue recovery applied to all domestic human tissue because of the potential for the transmission of communicable diseases. When the interim rule was published on December 14, 1993, there were no CLIA certified testing laboratories in foreign countries. Although these facilities were unavailable at the time, foreign establishments were not prohibited from using domestic CLIA certified laboratories for performing the required testing. Any laboratory, foreign or domestic, may apply for certification under CLIA. The proficiency of the laboratory performing the required testing is a key element in assuring the safety of human tissue. Inspection and regulation under CLIA helps to ensure that the laboratory is proficient and competent to perform the required tests accurately. Therefore, FDA's requirements are not intended to discriminate against foreign importers, but are an attempt to help ensure that foreign human tissue meets the same standards as human tissue procured in the United States for transplantation.

4. Plasma Dilution

20. Under section 1270.5(d) (§ 1270.21(h) of the final rule), human tissue from donors whose blood specimen may be diluted sufficiently to affect infectious disease test results is unsuitable unless the specimen is assessed for acceptability using an established procedure to calculate dilution (algorithm). One comment suggested revising the term ''hemodilution'' to ''plasma dilution'' to accurately describe the dilutional component because it is the infused plasma or fluid which dilutes the donor's plasma or serum used for testing, not the red cell volume.

FDA agrees with the comment and is amending § 1270.5(d)(1) § 1270.21(h)(2) in the final rule) to use the term ''plasma dilution.''

21. Two comments on § 1270.5(d) (§ 1270.21(h) of the final rule) proposed revisions to include specific factors for consideration in determining the suitability of human tissue when the possibility of plasma dilution exists. The comments noted that FDA did not address generally accepted criteria for making the determination of plasma dilution.

FDA recognizes that the interim rule did not address different factors such as amount of blood loss, renal output versus input of fluids, time of sampling in relation to transfusion/infusion, and volume transfused/infused in determining plasma dilution. Section 1270.21(h) of the final rule is revised to recognize that an algorithm may be used to ensure that there has not been plasma dilution sufficient to affect test results. Plasma dilution is further discussed in comment 25 of this document. FDA also notes that factors regarding the selection of an appropriate algorithm for determining plasma dilution are discussed in the Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation. The notice of availability of this guidance document may be found elsewhere in this issue of the **Federal Register**.

22. One comment on § 1270.5(d)(1) (§ 1270.21(g)(2)(i) of the final rule) inquired if a pretransfusion/infusion specimen was sufficient for testing or whether a posttransfusion/infusion specimen should also be tested.

A posttransfusion/infusion specimen is not necessary when an adequate pretransfusion/infusion specimen is available. If a pretransfusion/infusion specimen is unavailable for testing, then for the tissue to be assessed for suitability, a posttransfusion specimen must be assessed for plasma dilution using an algorithm prior to testing.

23. Five comments on § 1270.5(d)(1) (§ 1270.21(g)(2) of the final rule) discussed the difficulty in obtaining pretransfusion/infusion specimens because many potential donors arrive at the emergency room in the process of being transfused with blood or infused with fluids, thus eliminating the possibility of obtaining a pretransfusion/infusion specimen.

The agency realizes a pretransfusion/infusion specimen is not always available. In those cases where the specimen is unavailable, an algorithm to determine if plasma dilution may affect

test results should be applied to determine donor suitability. The establishment's standard operating procedures (SOP's) should outline this algorithm and the measures for determining donor suitability.

24. Two comments requested clarification of specific circumstances when plasma dilution should be considered and what specific tests would be affected by plasma dilution.

When a pretransfusion/infusion specimen is unavailable, FDA believes the following criteria should be considered in evaluating the need for using an algorithm to determine if plasma dilution is sufficient to affect infectious disease test results: (1) Blood loss is known or suspected to have occurred; (2) the tissue donor was transfused or infused and an adequate pretransfusion/infusion specimen is not available for infectious disease testing; (3) if preceding the collection of the donor specimen in adult donors, more than 2,000 milliliters (mL) of: whole blood, reconstituted blood, red blood cells, and/or colloids have been administered within the previous 48 hours and/or; crystalloids have been administered within the previous one hour; or any combination of these has occurred; and (4) in any donor 12 years of age or less, any transfusion/infusion has occurred. Once this information is reviewed and the determination is made that the 2,000 mL is exceeded or the donor is 12 years of age or less, the tissue is considered unsuitable until an algorithm defined in the tissue establishment's SOP's is used to assess whether the dilution affected the test results.

25. Fourteen comments on § 1270.5(d)(2) (§ 1270.21(h)(2)(ii) of the final rule) requested clarification and guidance on specific aspects of an acceptable algorithm in evaluating plasma dilution. One comment stated that, in the absence of science, further rulemaking should not include an arbitrary cutoff. In particular, the comments asked FDA to elaborate on: (1) Who is responsible for determining the parameters of the algorithm; (2) the type of blood, blood components, and fluids to be included or excluded; (3) the time period that is to be taken into consideration and the basis on which it is calculated; (4) the unit of measurement to be used; (5) the maximum volume allowed; and (6) the consideration given to output versus input.

FDA is not prescribing who may prepare the algorithm. It may be prepared by any responsible person with adequate training and understanding of the principles of plasma dilution. FDA discusses the criteria for using an algorithm to determine plasma dilution in comment 24 of this document, and is providing additional information on a suitable algorithm in the Guidance for Screening and Testing Donors of Human Tissue Intended for Transplantation announced elsewhere in this issue of the **Federal Register**. The information in the guidance document is based on available scientific evidence and was the focus of the workshop held in June 1995.

The discussion of an algorithm for determining plasma dilution in the guidance document is based on the calculation of blood volume and plasma volume in relation to the donor's body mass. Where blood loss has occurred or is suspected, and a pretransfusion/infusion donor specimen is not available,§ 1270.21(h) provides for use of an algorithm when the transfusion/infusion of more than 2,000 mL of whole blood, reconstituted blood, red blood cells, and/or colloids in the previous 48 hours and/or crystalloids within the previous one hour, or any combination, has occurred in the stated time periods prior to the collection of the specimen. The time periods recommended by the algorithm are based on the safety record of voluntary standards in the tissue industry employing such a time period and on a 50 percent volume dilution of blood or plasma. Transfused/infused products have been broken into categories for the purpose of calculating the volumes transfused/infused. They are blood, colloid, crystalloid, and a combination of these categories.

FDA believes and has included in the regulations at § 1270.21(h) that if the following conditions are exceeded in a circumstance of blood loss and replacement in an adult, or transfusion/infusion in a child 12 years of age or less, the tissue shall be determined not suitable for transplantation. The agency currently believes that transfusion/infusion of greater than one blood volume in the case of blood replacement or greater than one plasma volume in the case of colloid and crystalloid infusion, could make infectious disease testing results unreliable due to plasma dilution.

TABLE 2.—BLOOD AND PLASMA VOLUME CALCULATION

Category infused	Product(s) included in category	Hours prior to specimen collection	Calculated[1] volume administered
Blood	Blood unit labeled as ''Whole Blood,'' Blood unit labeled as ''Red Blood Cells,'' Reconstituted blood[2]	Within 48 hours	> one blood volume
Colloid	Plasma, platelets, albumin, hetastarch, dextran	Within 48 hours	> one plasma volume
Crystalloid	Saline, dextrose in water, Ringer's lactate, other balanced electrolyte solutions	Within 1 hour	> one plasma volume
Blood and colloids and/or crystalloids	See all of the above	Within 48 hours and within 1 hour	> one blood volume (or if the calculated volume for colloids only, within 48 hours of collection and/or crystalloids within 1 hour of collection is > one plasma volume)
Colloids and crystalloids	See above for colloid and crystalloid	Within 48 hours and within 1 hour	> one plasma volume

[1] Recommended methods for blood and plasma volume calculations may be found in the ''Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation.''

[2] Reconstituted blood means the extracorporeal resuspension of a blood unit labeled as ''Red Blood Cells'' by the addition of colloids and/or crystalloids to produce a hematocrit in the normal range.

5. Screening

26. Section 1270.5(e) (§ 1270.21(f) of the final rule) requires that in order to determine the suitability of human tissue for transplantation, the identity of the donor shall be ascertained and the relevant medical records shall be reviewed to assure freedom from risk factors for and clinical evidence of hepatitis B, hepatitis C, and HIV infection. One comment requested that the medical history include all available medical, coroner, and autopsy records, both written and those communicated orally by health care practitioners.

FDA agrees that oral communications specific to the donor's relevant medical history could affect donor suitability and should be documented because they are an integral part of the donor testing and screening process. This information should be recorded by a responsible person and should serve as an adjunct to other available information and records required by new § 1270.21. FDA has included a definition for ''relevant medical records'' in § 1270.3(t) which is consistent with the comment.

27. Twenty comments on § 1270.5(e) (§ 1270.21(f) and (g) of the final rule) expressed concern that the requirement for a donor medical history interview (formerly the Next-of-Kin interview in the interim rule) as part of the relevant medical records, would make it more difficult to procure corneas under legislative consent (formerly Medical Examiner Law in the interim rule and defined in § 1270.3(h) of the final rule). The comments suggested that the donor medical history interview for corneas procured under legislative consent be waived. One comment proposed using the ''all available information'' standard in determining suitability of corneas for transplantation. In an opposing viewpoint, six comments disagreed with a waiver of donor medical history interviews for corneas procured under legislative consent. The latter stated that corneas procured as a result of legislative consent do not meet industry standards and diminish the ability of transplant professionals to effectively promote the altruistic benefits of donation. These comments endorsed regulation of corneas because corneal tissue does transmit disease and should be regulated as strictly as other tissue.

After reviewing the numerous comments on the interim rule and the discussions at the workshops, FDA acknowledges the need for flexibility in the procurement of corneal tissue under legislative consent. Where corneas are procured under legislative consent, FDA has modified the regulations in the final rule to accept as sufficient a physical assessment of the donor in the absence of a donor medical history interview for behavioral and high risk information. Even though corneas may have a degree of protection due to avascularity, FDA notes that it is possible that viruses may be present in donor corneal tissue. Therefore, the agency believes that this modification underscores the importance of additional information gathering in determining the suitability of a donor. Negative viral marker test results for HIV and hepatitis, and review of other available information in addition to the physical assessment, will continue to be a requirement. However, if additional tissue other than cornea is recovered from the same donor, then a donor medical history interview is required. Based on the recommendation of the PHS ''Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs'', (MMWR, May 20, 1994) FDA is requiring under new § 1270.21(g) documentation in the summary of records that corneal tissue was procured under legislative consent so that the transplant surgeon will be aware that: (1) A donor medical history interview was not obtained, (2) a physical assessment of the donor for evidence of high risk behavioral signs of HIV and hepatitis infection had been made, and (3) the tissue was determined to be suitable in the absence of the donor medical history interview.

28. One comment on § 1270.5(f) (§ 1270.21(e) of the final rule) stated that the requirement that a full set of records physically accompany each of the approximately 300,000 allografts distributed annually in the United States was superfluous as well as unduly burdensome and expensive.

FDA believes that the comment has misinterpreted the meaning of § 1270.5(f). Human tissue that is determined to be suitable for transplantation per § 1270.9(b) (§ 1270.21(e) of the final rule) must be accompanied by copies of original records, indicating that all infectious disease testing and screening under § 1270.5 (§ 1270.21 of the final rule) has been completed, reviewed by the responsible person, and found to be negative. The agency has routinely accepted completed summaries of such records as long as the summary contains the identity of the testing laboratory, the listing and interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records, and the name of the person or establishment determining the suitability of the human tissue for transplantation.

After review, FDA finds the recordkeeping requirements of the rule no more burdensome or potentially costly than the standards established by the American Association of Tissue Banks or the Eye Bank Association of America which require labeling and package inserts to accompany a shipment of human tissue.

6. Written Procedures (§ 1270.31)

Section 1270.7 (§ 1270.31 of the final rule) sets forth the requirements for written procedures for infectious disease testing, and obtaining, reviewing, and assessing the relevant medical records of the donor.

The agency has added § 1270.31(c) and (d) requiring written procedures for the designation and identification of quarantined tissue, and for the prevention of contamination or cross-contamination of tissues during processing. Because HIV and hepatitis screening and testing of the donor may be incomplete at the time of processing, and to maintain the separation of suitable tissue from that not yet determined to be suitable or tissue that has been determined to be unsuitable for transplantation (which is the intent of the concept of ''quarantine'' as it is used in the final rule), FDA is requiring that these written procedures be prepared and followed. FDA is also requiring that the written procedures for preventing the contamination or cross-contamination by tissues during processing be validated. These requirements will facilitate the timely processing of tissue when necessary (e.g., skin and cornea) while maintaining quarantine and continuing current good practices performed by industry in daily processing.

29. Two comments asked for a clearer statement that the written procedures and records requirement of §§ 1270.7(a) and 1270.9(a) are the responsibility of the laboratory where the tests are run.

FDA has amended the requirements of § 1270.9 (§ 1270.33 of the final rule) to state that the person or establishment making the determination regarding the suitability of human tissue is responsible for retaining all testing and screening records used in making the

determination of suitability for transplantation. FDA believes that the person (as defined in § 1270.3(m) of the final rule) or establishment (as defined in § 1270.3(i) of the final rule) that has made the determination of suitability should have and retain the testing and screening records used in making the determination. The individual records must also be retained by the establishment performing the work being recorded. For human tissue that is determined to be suitable, the person or establishment receiving the human tissue should receive a summary of records (as described in § 1270.1(w)) used in determining the suitability of the donor. The summary should identify the responsible person, in addition to the person or establishment that made the determination that the human tissue is suitable for transplantation in accordance with § 1270.21(e). Other than having the summary, FDA does not expect the transplant institution to receive complete documentation regarding the suitability of the donor. If FDA has questions regarding donor suitability, the person or establishment that made the determination of donor suitability will ordinarily be contacted. That person or establishment is responsible for having all records used in making the determination. With respect to testing records, the testing laboratory should retain records of the test results and the interpretation of the test results. Copies of the interpretation of the test results should also be provided to, and retained by, the person or establishment making the final determination of donor suitability.

30. Three comments on § 1270.7(c) (§ 1270.31 of the final rule) requested clarification on which organization's SOP would be acceptable and suggested that the agency require each facility to have its own SOP that includes processing, storage, and final disposition of human tissue.

The regulations require each facility to prepare and follow written procedures for testing and screening of human tissue. In § 1270.31 of the final rule, written procedures are required for all significant steps involved in the infectious disease testing process which shall conform to the manufacturers' instructions for use contained in the package inserts, and for all significant steps in obtaining, reviewing, and assessing for completeness the relevant medical records of the donor. Any deviation from the establishment's written procedures shall be recorded and justified. FDA investigators review an establishment's written procedures during an inspection, to evaluate whether the SOP's are consistent with the regulations, and to determine that the establishment is following the procedures documented in the SOP's. A detailed and complete SOP ensures uniformity and consistency for each procedure performed. Each establishment may develop its own written procedures or adopt those in a manual prepared by another organization, as long as the procedures satisfy the requirements set out in the regulations. Because each establishment differs, an establishment using procedures developed by another establishment or organization should evaluate those procedures to determine whether they are adequate or need to be revised by that establishment. The responsibility for ensuring adequacy of procedures and compliance rests with the individual establishment regardless of the source of its procedures.

7. Records, general requirements (§ 1270.33) and Specific records (§ 1270.35)

Sections 1270.9 and 1270.11 of the interim rule (§§ 1270.33 and 1270.35, respectively of the final rule) set forth the general and specific requirements for the maintenance of records. Under § 1270.33(c), all human tissue that is to be processed or shipped prior to the determination of donor suitability must be under quarantine, accompanied by records identifying the donor, and identifying the tissue as not determined to be suitable for transplantation. All human tissue found suitable for transplantation must be accompanied by a complete summary of records, or copies of the original records, documenting that all infectious disease testing and screening has been completed, reviewed by the responsible person, and identified as determined to be suitable for transplantation. The summary of records also lists all the available records used in determining the suitability of the donor so that the originals of these records can be accessed, if necessary. These records include the donor medical history interview, the relationship of the person interviewed to the donor, the physical assessment of the donor, autopsy or coroner records, hospital records, police records, and any other available record used to document the suitability of the donor. If only corneal tissue was procured under legislative consent in the absence of a donor medical history interview, the accompanying summary of records shall document that: (1) A donor medical history interview was not obtained; (2) a physical assessment of the donor for evidence of high risk behavior and signs of HIV and hepatitis infection had been made; and (3) the tissue was determined to be suitable in the absence of the donor medical history interview. Under § 1270.9(c) (§ 1270.33(f) of the final rule) the person or establishment making the determination regarding the suitability of human tissue is responsible for retaining the completed records and making them available to FDA upon their request.

Section 1270.35(c) of the final rule has been added to complete the accounting of the inventory between determination of suitability (§ 1270.35(a) and (b)) and the final disposition of the human tissue (§ 1270.35(d)), e.g., the destruction of unsuitable tissue, nonclinical research use, or distributed for transplantation. The interim rule required the documentation of the records used in determining the suitability of the human tissue, and the destruction or disposition of unsuitable human tissue. The final rule requires in § 1270.35(c) documentation of the receipt and/or distribution of human tissue.

31. One comment recommended that the facility that made the final determination of donor suitability and retrieved the human tissue be required to maintain the medical history and testing records for each donor.

Retrieval and determination of donor suitability are often done by separate facilities, therefore, FDA has modified the language in § 1270.9(c) (§ 1270.33(f) of the final rule) to require the maintenance of records under § 1270.5 (§ 1270.21 of the final rule), including all testing and screening records, by the person or establishment making the determination regarding the suitability of human tissue. Persons or establishments performing operations that would generate documentation that has a bearing on a donor's suitability would retain that documentation and make it available during an FDA authorized inspection.

32. Two comments urged FDA to continue to require record retention for 10 years or until the expiration date of the human tissue, which could be longer than 10 years, but in any event no less than 10 years.

FDA agrees with the comments and has modified § 1270.33(h) to require the retention of records for a period that extends at least 10 years beyond the date of transplantation, if known, distribution, disposition, or expiration of any dating period related to the human tissue, whichever is latest.

33. One comment stated that the definition for required exclusions due to the presence of risk behaviors for certain diseases should be at all times consonant with the recommendations of

the CDC and the human tissue bank professions.

FDA has developed guidance on behavioral and high risk information, taking both the CDC's recommendations and those of the human tissue bank professions into account. At the June 1995 workshop, FDA distributed a draft document, which was also made available to the general public, discussing screening and testing issues. Representatives from CDC participated in all three workshops and FDA has based its recommendations for testing and screening on the PHS guidelines published in the *Morbidity and Mortality Weekly Reports* of April 1991, and May 1994 and public comment submitted in response to the workshop.

In conjunction with this rule, FDA is issuing a guidance document concerning the screening and testing of donors of human tissue intended for transplantation. FDA developed this document taking into account the recommendations of PHS, the Medical Standards of the Eye Bank Association of America, the American Association of Tissue Banks and comments from other interested persons.

8. Inspections (§ 1270.41)

Section 1270.13 (§ 1270.41 of the final rule) addresses the inspectional process. Establishments covered by the regulations include those establishments that recover, screen, test, process, store, or distribute human tissue and include those establishments performing such activities under contract. In large part, inspections of tissue establishments are conducted in the same manner as inspections of firms dealing in other FDA regulated commodities. FDA is presently assessing its inspectional procedures and the extent to which the agency can work with other qualified organizations to make best use of limited resources.

FDA investigators cover several major areas during an inspection. All facilities are subject to examination, including any facility contracted by the primary facility such as testing laboratories, contract sterilizers, or off-site storage facilities. The investigators may examine any human tissue at the firm to observe, for example, whether it is appropriately quarantined, identified, and stored. The inspections generally will focus on a review of required records. Employees may be interviewed regarding their performance of regulated activities. At the end of the inspection, if possible violations of the regulations are found, the FDA investigator will issue to the responsible person at the establishment a list of ''Inspectional Observations'' (Form FDA–483), describing the observations of the investigator that represent an observed or potential problem with the facility or tissue. After the report of the investigator is reviewed, FDA may issue additional correspondence to the establishment describing the violations to the regulations and requesting appropriate followup action.

FDA intends to continue to inspect regulated establishments, both foreign and domestic, when deemed necessary by the agency to ensure that human tissue is screened and tested to reduce risk of HIV, hepatitis B, or hepatitis C. Frequency of inspection after an initial inspection may depend on the extent of any violations found and will be at the agency's discretion.

34. One comment on § 1270.13 (§ 1270.41 of the final rule) asserted that the provision which allows investigators to question personnel of the establishment as the investigator deems necessary is inappropriate under the governing case law. The comment cited *Donovan* v. *Dewey*, 452 U.S. 594 (1981); *Stark* v. *Wickard*, 321 U.S. 559 (1944), and *Ernst* v. *Hochfelder*, 425 U.S. 185 (1976) to support this assertion.

FDA disagrees with the interpretation of these three cases in the context of the governing statutory authority, the PHS Act. Section 361 of the PHS Act authorizes the Secretary to issue and enforce regulations to control communicable diseases, and it provides for such inspection and destruction of articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, that may be necessary. These other measures include the use of routine inspections and the questioning of personnel during such inspections. The FDA inspector may question the firm's personnel to determine if the staff is familiar with and following the firm's written SOP's.

35. One comment on § 1270.13(e) (redesignated as § 1270.41(e) of the final rule) asked FDA to clarify whether the FDA investigator or a human tissue bank official is responsible for ensuring that records to be copied are suitably expurgated. The comment also asked for guidance on the scope and meaning of ''suitably.''

FDA has revised § 1270.41(e) of the final rule to clarify that FDA will follow its existing procedures regarding disclosure of documents. Under these procedures, FDA takes necessary precautions to protect the privacy of names of tissue donors or recipients prior to public disclosure. These procedures are set forth in 21 CFR part 20. See e.g., 21 CFR 20.63. FDA recognizes the sensitive nature of the information that would identify a human tissue donor or recipient. FDA may copy records containing identification of the donors or recipients if such records are needed for example, to document the distribution of potentially infectious human tissue.

9. Human Tissue Offered For Import (§ 1270.42)

Because some human tissue used for transplantation in the United States is obtained from foreign sources or is processed in foreign facilities and because of requests for clarification of requirements for such tissue, FDA has added § 1270.42 to clarify the administrative steps for the importation of tissue into the United States. Human tissue that has been recovered from sources outside the United States can enter the country, and tissue that has been recovered from sources in the United States that has been sent outside the United States for processing can reenter the country consistent with the provisions of §§ 1270.33 and 1270.42. For tissue imported prior to the determination of donor suitability, the tissue must be accompanied by records assuring identification of the donor and indicating that the tissue has not been determined to be suitable for transplantation. For tissue determined to be suitable for transplantation, the tissue is to be accompanied by a summary of records, or copies of the original records, indicating that all infectious disease testing and screening under § 1270.21 has been completed, reviewed by the responsible person, and found to be negative. Tissue that has been determined to be suitable for transplantation must also be identified. As with other imports, the importer of record (as defined in § 1270.3(k) of the final rule) for human tissue must notify the District Director of FDA having jurisdiction over the port of entry when the articles are offered for import. The tissue must be held in quarantine until and unless the article is released by FDA. Human tissue that is offered for import and is found to be in violation of part 1270, is subject to recall and destruction in accordance with § 1270.43 of the final rule.

10. Retention, Recall, and Destruction of Human Tissue (§ 1270.43)

Section 1270.15 of the interim rule (§ 1270.43 of the final rule) describes the procedures for the retention, recall, and destruction of human tissue upon a finding that the human tissue may be in violation of the regulations.

36. One comment on § 1270.15 (§ 1270.43 of the final rule) requested that the rule be clarified to state that

when a part 16 (21 CFR part 16) hearing has been requested, human tissues need not be destroyed until the hearing is held.

FDA has clarified § 1270.43(e) to state that any possible destruction of human tissue would be held in abeyance pending resolution of the hearing request. Under the provisions of § 16.24(d), the Commissioner of Food and Drugs (the Commissioner) may take action pending a hearing that is necessary to protect the public health. FDA is, however, sensitive to the potential economic consequences that would result from the immediate destruction of potentially violative human tissue. Any human tissue listed in such an order must be held in quarantine and cannot be released prior to the resolution of a hearing request and receipt of written notice from FDA. If destruction is warranted, the destruction of the human tissue is to be conducted under the supervision of a designated FDA official.

37. One comment asked that FDA clarify the ''may be in violation'' language in the recall and destruction part of the rule, particularly with respect to what triggers the finding of a violation.

The procedures for retention, recall, and destruction in § 1270.43 will be used only when the agency deems it necessary to ensure the suitability of human tissue for transplantation. FDA intends to invoke § 1270.43 of the final rule when there is evidence of a violation related to tissue suitability, such as the source of the human tissue, the adequacy of the testing or screening of the human tissue, the completeness of the records accompanying the human tissue, the adequacy of donor selection, and/or the attention given to the possibility that the donor was at a high risk for HIV or hepatitis.

C. Comments on Legal Issues

38. Five comments objected to the immediate effective date of the interim rule and questioned why such a measure was taken. Four comments objected to the required retrospective application of the interim rule, in that it applied to human tissue in storage upon the effective date, which may have been collected and tested before the effective date of the interim rule.

The Administrative Procedure Act (the APA) (5 U.S.C. 551 *et. seq.*) governs the issuance of rules by executive agencies. The APA's requirement of notice and comment prior to the implementation of a rule may be dispensed with when the agency for ''good cause'' finds that the procedures are ''impracticable, unnecessary, or contrary to the public interest.'' (See 5 U.S.C. 553(b)(B).)

In the preamble to the interim rule (58 FR 65514 at 65518), FDA described its good cause for proceeding directly to an interim rule. Specifically, the agency stated that the Commissioner found that the use of prior notice and comment rulemaking was ''contrary to the public interest'' because of the ''unnecessary risk of transmission of HIV infection and hepatitis infection from shipment and transplantation of human tissues derived from inadequately tested or screened donors.'' During an investigation prior to the promulgation of the interim rule, FDA investigators learned of the availability, importation, and distribution of musculoskeletal tissue materials that had not been adequately screened or tested for HIV, hepatitis B, and hepatitis C. This investigation illustrated the need for swift action to reduce the risk to the public health. Because of the public health risk posed by the inadequately tested or screened tissues, FDA applied the regulations not only to tissues screened after the effective date but also to human tissue remaining in storage for transplantation.

As previously stated, FDA provided opportunities for public comment following the promulgation of the interim rule and has considered those comments and the agency's experience in developing the final rule.

The final rule will have an effective date of 180 days after the date of publication and will apply to human tissue intended for transplantation procured on or after the effective date. For tissue procured prior to the effective date of the final rule, the interim rule applies.

39. One comment urged Federal preemption of State and local regulations on donor suitability, testing and labeling of human tissues.

FDA declines to take such a measure because the agency is not aware of any compelling reason that State regulatory authorities should be preempted at this time. The rule provides the minimum criteria necessary to help ensure tissue safety, and States are free to add additional requirements that they believe are warranted.

D. Comments on Economic Issues

40. Two comments on the economic impact in the preamble to the interim rule stated that the rule would result in an increase in the human tissue processing fee that the recipient must pay. In addition, one of the two comments stated that the number of human tissue transplants mentioned by the agency may be inaccurate and human tissue banking activities generate $59 million rather than $100 million per year.

FDA has considered the data provided in these comments in finalizing the regulations. The comments did not, however, provide the agency with figures that would illustrate an increase in the human tissue processing fee.

41. Three comments stated that the implementation of the regulations will drive the cost of corneal transplant beyond the means of the average person.

These comments did not provide data to support their contention. FDA's intention is to make tissue that is available for transplantation safer. The Eye Bank Association of America Statistical Report for 1994 does not support the premise that there has been any decrease in the availability or transplantation of corneal tissue. Both the total number of donations and the total number of transplants have increased during 1994 under the Interim Rule. However, as discussed in comment 27, FDA acknowledges the need for flexibility and has modified the requirement for corneas procured under legislative consent when there is no medical history interview available.

E. Requests for Additional Regulations

42. Five comments asked FDA to regulate all human tissue banking efforts including musculoskeletal, skin, eye, reproductive tissue, blood vessel, bone marrow, heart valves, and hospital surgical bone banks.

This rule does not apply to reproductive tissue, bone marrow, human milk, and heart valves under part 1270. Heart valves are already regulated by FDA as medical devices. HRSA administers the program for the National Bone Marrow Donor Registry. As noted in comment No. 8, in the near future, FDA is considering proposing additional regulations governing the use of human tissue and is considering whether to expand the scope of the rule to cover additional tissues.

43. Three comments stated that all tissue banks, despite their type, should be federally registered and subject to inspection and accreditation. One additional comment urged FDA to consider the use of a nongovernmental organization as a private accrediting and/or inspecting entity.

FDA declines to adopt the suggestions made by these comments as they relate to registration and accreditation at this time, as they are outside the scope of the rule, but is considering addressing registration and accreditation in future rulemaking, at which time comments will be solicited. Tissue facilities that are regulated under the provisions of the

interim rule are subject to and will continue to be subject to Federal inspection under the final rule.

44. One comment suggested that tissue banks should bank and hold serum specimens from donors for 5 years beyond the expiration date of the human tissue allograft for additional testing that may become relevant to public health in the future.

The comment did not provide any demonstrable evidence that such a practice is necessary for the protection of the public health. In the absence of such evidence, FDA declines to add such a requirement. Complete and careful donor screening and testing in accordance with the provisions of the rule, as well as maintenance of records for the period specified in § 1270.33(h) should provide sufficient information to investigate possible transmission of infectious disease. FDA is willing to consider evidence that such a requirement is warranted.

45. One comment urged a requirement that records show the destination of all human tissue released for transplant.

FDA is requiring disposition records for human tissue (distribution for transplantation, use for nonclinical research, or destruction) but is not requiring tracking to the recipient at this time. FDA is considering requirements for the tracking of human tissue for inclusion in future rulemaking. FDA discussed the tracking of human tissue under a Federal regulatory scheme with members of the industry at both the March 1995 and June 1995 workshops described earlier. FDA notes that currently the voluntary standards of the American Association of Tissue Banks and the Eye Bank Association of America include the tracking of human tissue from the donor to the recipient, transplanting surgeon or institution.

46. Three comments requested FDA to consider developing requirements for discussing donor medical history with the Next of Kin or others who might sign the donation consent form.

FDA recognizes the requests for requiring a donor medical history interview, and the need for guidance in conducting the donor medical history interview for assurance that the donor did not participate in high risk behavior for hepatitis and HIV infection. The donor medical history interview is an integral part of the relevant medical records and is defined as such in the final rule. FDA is announcing the availability of ''Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation'' elsewhere in this **Federal Register** to assist those facilities involved in determining the suitability of a donor.

47. Two comments inquired about the mechanism used by FDA in requiring new tests in the future and deleting obsolete tests, and added that a careful evaluation and decision analysis should consider the test's specificity, sensitivity, and positive utility.

It is the practice of FDA to thoroughly evaluate all data including that accumulated by its scientists, by industry scientists, and by academicians when considering the use of a test or deletion of a test for communicable disease. When appropriate, FDA presents such data to an advisory committee composed of specialists and requests their recommendation. Therefore, FDA evaluates the need to add or delete a test for communicable disease taking into account the available scientific data and the effect of the test on the public health.

48. One comment inquired as to the suitability of an umbilical cord blood specimen or the mother's blood specimen for viral marker testing on newborn donors.

To date, none of the viral marker test kits address cord blood as an adequate sample in the package insert. Cord blood may not be acceptable for testing if contamination of the specimen with Wharton's jelly occurs during collection. If an adequate cord blood specimen is not available, then the mother's blood specimen will be considered acceptable for testing. FDA has added § 1270.21(b) to the final rule to clarify that in the case of a neonate, the mother's specimen is acceptable for testing.

F. Comments on New Regulatory Areas

49. Forty-four comments were also received that were beyond the scope of this rulemaking. For example, five comments expressed concern that FDA would require user fees to fund the regulation of human tissue.

This final rule does not impose a user fee requirement for human tissue. User fee authority to fund tissue banking regulation was presented in legislation introduced by Representative Wyden in H.R. 3547 and Senator Simon in S. 1702 during the 1994 Congressional term. Neither bill was passed.

50. One comment stated that it would be appropriate to include recordkeeping and tracking requirements for hospitals and other transplant facilities.

FDA at this time declines to incorporate tracking requirements in this rule. Promulgation of tracking requirements would affect transplant facilities currently not within the scope of the final rule, unless they are involved in recovery, screening, testing, processing, or distribution of human tissue. In this rulemaking, FDA is not expanding the recordkeeping requirements beyond those in § 1270.35(c), or otherwise revising significantly its regulatory program on human tissue at this time. The comments are being considered as FDA reviews the possibility of further developing its regulatory program and may be the subject of future rulemaking.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The agency has also determined that this rule is a significant regulatory action under paragraph (f)(4) of the Executive Order because it raises novel policy issues.

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 below, the agency certifies that this rule will not have a significant impact on a substantial number of small entities.

A. The Need For the Regulation

The purpose of the final rule is to provide clarification of the interim rule, revise the rule in response to public comments, and finalize its provisions. The interim rule was promulgated as an emergency measure to protect the public safety against human tissue that had incomplete or no documentation ascertaining its freedom from communicable diseases. This risk was clearly demonstrated by evidence of human tissue from foreign sources that had been offered for sale in the United States with little documentation of appropriate screening and testing. The final rule takes into account comments submitted to the Dockets Management Branch, and discussions and information obtained through public participation in three workshops held following the promulgation of the interim rule. The objective of the final rule is to impose minimal requirements for testing and screening of human

tissue donors, while making all human tissue, imported and domestic, safe for transplant needs.

B. A Description of Requirements

The interim rule requires all facilities to ensure that specified minimum required medical screening and infectious disease testing has been performed and that records documenting such screening and testing for each human tissue are available for inspection by FDA. The final rule clarifies and modifies requirements in the interim rule and adds three additional requirements, which are currently voluntary industry standards: written procedures for the designation and identification of quarantined tissue (§ 1270.31(c)); written and validated procedures for the prevention of contamination or cross-contamination of tissues during processing (§ 1270.31(d)); and documentation of receipt and/or distribution of human tissue determined to be suitable for transplantation until it is distributed to the transplanting facility (section 1270.35(c)).

C. The Type and Number of Firms Affected

The rule will affect any establishment or person engaged in the recovery, screening, testing, processing, storage or distribution of human tissues. Because of their small size, tissue specialty, and/or interrelationship with other tissue establishments, most tissue establishments do not perform all of these activities. Thus, the effect of this rule will vary depending on the number and type of functions performed. Because tissue establishments are not currently required to register with FDA, the agency does not have a precise count of the number of establishments that will be affected by this rule. EBAA reports 110 member eye banks. Also, an FDA/HRSA sponsored survey projected that in 1994, about 67 tissue banks procured musculoskeletal tissue from cadaveric donors. (Jeffrey Prottas, (1995) ''A Study of the Tissue Procurement and Distribution System of the United States''). This survey also projected an additional 120 surgical bone banks, entities which typically involved one or more surgeons who save and freeze for later use bone obtained during routine surgical procedures. There also may exist an unknown number of uncounted skin banks. (Neither of these latter two groups—surgical bone and skin banks—are believed to account for substantial volume of tissue.) All together, therefore, FDA estimates that the rule may affect a total of about 400 establishments. Since the majority of these establishments employ fewer than 15 employees, the Small Business Administration would define almost all as small entities.

D. Nature of Impact

FDA finds that the final rule will have little adverse impact on the tissue industry. When issuing the interim rule, FDA took voluntary industry standards and State requirements into account to minimize the impact on the supply of tissue available for transplantation and to reduce the economic burden to industry. In its preamble to the interim regulation (58 FR 65519), FDA determined that the only economic impact of the rule would be related to the recordkeeping burdens, ''because the cost of testing for infectious disease and the cost of screening donors has already been assumed by the tissue banking industry and this interim rule imposes no additional burdens.'' The agency has received no new industry comment that would alter its conclusion that donor testing and screening are universally accepted practice for the industry.

The eye bank sector, however, has questioned the need for the potential burden associated with certain aspects of the interim donor screening requirements. Several comments suggested that the agency exempt corneas from regulations due to an adequate safety record and adequate internal standards (Comment 3). Some asked that the agency exempt these operations from the requirement for a donor medical history interview as part of the relevant medical record, if the document was not available; stating that this requirement makes it more difficult to procure corneas under legislative consent (Comment 27).

FDA has given great consideration to the impact that such changes would have on both the tissue establishments and the public health. The agency believes that all human tissues have the potential to transmit communicable diseases and that every reasonable effort should be made to prevent disease transmission, while ensuring the continued availability of safe human tissue. Keeping these elements in focus, FDA decided to regulate all human tissue under the same standards (protecting the public health by preventing disease transmission), while permitting the procurement of corneas under legislative consent when a donor medical history interview is not available. Thus, the final FDA rule allows greater flexibility in the procurement of corneal tissue under legislative consent, while minimizing any potential regulatory burden.

Similarly, the new requirements of the final rule, (e.g., preparing two standard operating procedures and increased documentation for receipt and/or distribution of human tissue) will not add significantly to operating costs. The final requirements are part of industry voluntary standards and therefore, are currently in place in most tissue banks. The 60 tissue banks and 110 eye banks that are currently members of the AATB and the EBAA, respectively, are likely to account for the great majority of tissue transactions. For those few establishments that do not have or must modify their existing written procedures, FDA estimates that they will require a one-time expenditure of approximately 7 hours for each of four required written SOP's. Furthermore, since the smaller tissue banks would be unlikely to process tissue (the Prottas survey projects that only 28 percent of the 67 musculoskeletal banks process tissue), the smaller tissue banks will need to prepare only three written procedures.

Likewise, the new requirements for documenting the distribution and receipt of human tissue will impose few costs. Prottas found that 95 percent of the surveyed musculoskeletal banks could track tissue to recipient institutions. These banks presumably already identify and document their products. Although the smallest tissue banks may need to expand this effort, the associated cost would be mitigated by the smaller number of transactions at such establishments.

In sum, the final rule sets minimal requirements to prevent the transmission of communicable diseases from human tissue used for transplantation. The vast majority of tissue establishments were voluntarily complying with most of the requirements of the interim rule before it was issued, and are voluntarily complying with the new requirements in this final rule. As described in Section V of this document, some entities may need to prepare or modify existing documentation procedures, but FDA believes that very few will need to alter actual operations. At almost no establishment would additional reporting and recordkeeping activities take over 20 hours of time annually for a nurse, physician assistant, or certified technician. As a result, FDA expects that very few entities will incur significant costs due to this rule. FDA therefore certifies that this rule will not have a significant impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

Although the December 14, 1993, interim rule (58 FR 65514) provided a 90-day comment period under the Paperwork Reduction Act of 1980, and this final rule responds to the comments received, FDA is providing an additional opportunity for public comment under the Paperwork Reduction Act of 1995, which was enacted after the expiration of the comment period and applies to this final rule. Therefore, FDA now invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology. Individuals and organizations may submit comments on the information collection provisions of this final rule by September 29, 1997. Comments should be directed to the Dockets Management Branch (address above).

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review and approval. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions. 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.

This final rule contains information collection requirements which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995. The title, description, and respondents of the information collections are shown below with an estimate of the annual recordkeeping and periodic reporting burden.

Title: Human Tissue Intended for Transplantation: 21 CFR part 1270.

Description: FDA is issuing final regulations to prevent the transmission of HIV, hepatitis B, and hepatitis C through the use of human tissue for transplantation. The final regulations closely parallel those contained in the interim rule on human tissue intended for transplantation. Both the interim and final rule provide for inspection by FDA of persons and tissue establishments engaged in the recovery, screening, testing, processing, storage, or distribution of human tissue. These facilities are required to meet standards intended to ensure appropriate screening and testing of human tissue donors and ensure that records are kept documenting that the appropriate screening and testing have been completed.

Description of Respondents: Businesses or other for-profit; nonprofit institutions; small businesses or organizations.

There are approximately 60 tissue establishments with 300 employees that are members of the American Association of Tissue Banks. There are an additional 600 individual members of which 50 percent are performing a tissue banking activity. The Eye Bank Association of America's membership consists of 120 eye banks of which 110 are in the continental United States.

With the rare exceptions noted in the preamble, FDA believes that all respondents perform donor testing and screening for HIV and hepatitis and these regulations add no additional requirements. New § 1270.31(c) and (d) require written procedures for the designation and identification of quarantined tissue and to prevent the contamination or cross-contamination of tissue during processing. Section 1270.35(c) requires documentation of the distribution and receipt of human tissue, completing the accounting of tissue between determination of suitability, and the destruction or disposition of the tissue.

When the interim rule was promulgated, accredited members of the American Association of Tissue Banks and the Eye Bank Association of America were already in compliance with the regulations by adhering to the standards established by these organizations. The requirements added to the Final Rule will not impose additional burden since the members will be complying with the current organizations' standards which are comparable to the requirements in the final rule. To account for persons or establishments that may not be a member of an industry organization and, for whom therefore, the extent of compliance with the requirements of the final rule is unknown, FDA will be using 1 percent as an estimation of the information collection burden on the tissue industry.

Industry estimates that in 1994 there were 350,000 bone transplants, 42,000 corneal transplants, 5,000 patellar tendon transplants, and the transplantation of 5,000 square feet of skin. There are approximately 300 persons and 170 tissue banks currently operating in the United States affected by the regulations.

TABLE 3.—ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
1270.31(a) and 1270.31(b) and 1270.31(c) and 1270.31(d)	11	4	44	28	308
1270.35(a) and 1270.35(b)	11	420	4,620	290	3,190
1270.35(c)	11	2,893	31,823	4,782	52,602
1270.35(d)	11	17	187	17	187
Total					56,287

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 1270

Communicable diseases, HIV/AIDS, Reporting and recordkeeping requirements.

Therefore, under the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 16 and 1270 are amended as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. The authority citation for 21 CFR part 16 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–394); 21 U.S.C. 41–50, 141–149, 467f, 679, 821, 1034; secs. 2, 351, 361 of the Public Health Service Act (42 U.S.C. 201, 262, 264); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 28 U.S.C. 2112.

2. Section 16.1 is amended in paragraph (b)(2) by revising the entry for ''§ 1270.15(e) * * *'' to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * *

§ 1270.15(e), relating to the retention, recall, and destruction of human tissue.

3. Part 1270 is revised to read as follows:

PART 1270—HUMAN TISSUE INTENDED FOR TRANSPLANTATION

Subpart A—General Provisions

Sec.

Subpart B—Donor Screening and Testing

Subpart C—Procedures and Records

Subpart D—Inspection of Tissue Establishments

Authority: Secs. 215, 311, 361, 368 of the Public Health Service Act (42 U.S.C. 216, 243, 264, 271).

Subpart A—General Provisions

§ 1270.1 Scope.

(a) The regulations in this part apply to human tissue and to establishments or persons engaged in the recovery, screening, testing, processing, storage, or distribution of human tissue.

(b) Regulations in this chapter as they apply to drugs, biologics, devices, or other FDA-regulated commodities do not apply to human tissue, except as specified in this part.

(c) Regulations in this chapter do not apply to autologous human tissue.

(d) Regulations in this chapter do not apply to hospitals or other clinical facilities that receive and store human tissue only for transplantation within the same facility.

§ 1270.3 Definitions.

(a) *Act* for the purpose of this part means the Public Health Service Act, section 361 (42 U.S.C. 264).

(b) *Blood component* means any part of a single-donor unit of blood separated by physical or mechanical means.

(c) *Colloid* means a protein or polysaccharide solution that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment such as albumin, dextran, hetastarch; or certain blood components, such as plasma and platelets.

(d) *Contract services* are those functions pertaining to the recovery, screening, testing, processing, storage, or distribution of human tissue that another establishment agrees to perform for a tissue establishment.

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

(f) *Distribution* includes any transfer or shipment of human tissue (including importation or exportation), whether or not such transfer or shipment is entirely intrastate and whether or not possession of the tissue is taken.

(g) *Donor* means a human being, living or dead, who is the source of tissue for transplantation.

(h) *Donor medical history interview* means a documented dialogue with an individual or individuals who would be knowledgeable of the donor's relevant medical history and social behavior; such as the donor if living, the next of kin, the nearest available relative, a member of the donor's household, other individual with an affinity relationship, and/or the primary treating physician. The relevant social history includes questions to elicit whether or not the donor met certain descriptions or engaged in certain activities or behaviors considered to place such an individual at increased risk for HIV and hepatitis.

(i) *Establishment* means any facility under one management including all locations, that engages in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation.

(j) *Human tissue* means any tissue derived from a human body, which:

(1) Is intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease;

(2) Is recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics;

(3) Is not currently regulated as a human drug, biological product, or medical device;

(4) Excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ; and

(5) Excludes semen or other reproductive tissue, human milk, and bone marrow.

(k) *Importer of record* means the person, establishment or their representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

(l) *Legislative consent* means relating to any of the laws of the various States that allow the medical examiner or coroner to procure corneal tissue in the absence of consent of the donor's next-of-kin.

(m) *Person* includes an individual, partnership, corporation, association, or other legal entity.

(n) *Physical assessment* means a limited autopsy or recent antemortem or postmortem physical examination of the donor to assess for any signs of HIV and hepatitis infection or signs suggestive of any risk factor for such infections.

(o) *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.

(p) *Processing* means any activity performed on tissue, other than tissue recovery, including preparation, preservation for storage, and/or removal from storage to assure the quality and/or sterility of human tissue. Processing includes steps to inactivate and remove adventitious agents.

(q) *Quarantine* means the identification of human tissue as not suitable for transplantation, including human tissue that has not yet been characterized as being suitable for

transplantation. Quarantine includes the storage of such tissue in an area clearly identified for such use, or other procedures, such as automated designation, for prevention of release of such tissue for transplantation.

(r) *Reconstituted blood* means the extracorporeal resuspension of a blood unit labeled as ''Red Blood Cells'' by the addition of colloids and/or crystalloids to produce a hematocrit in the normal range.

(s) *Recovery* means the obtaining from a donor of tissue that is intended for use in human transplantation.

(t) *Relevant medical records* means a collection of documents including a donor medical history interview, a physical assessment of the donor, laboratory test results, medical records, existing coroner and autopsy reports, or information obtained from any source or records which may pertain to donor suitability regarding high risk behaviors, clinical signs and symptoms for HIV and hepatitis, and treatments related to medical conditions suggestive of such risk.

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

(v) *Storage* means holding tissue.

(w) *Summary of records* means a condensed version of the required testing and screening records that contains the identity of the testing laboratory, the listing and interpretation of all required infectious disease tests, and a listing of the documents reviewed as part of the relevant medical records, and the name of the person or establishment determining the suitability of the human tissue for transplantation.

(x) *Vascularized* means containing the original blood vessels which are intended to carry blood after transplantation.

Subpart B—Donor Screening and Testing

§ 1270.21 Determination of donor suitability for human tissue intended for transplantation.

(a) Donor specimens shall be tested for the following communicable viruses, using Food and Drug Administration (FDA) licensed donor screening tests in accordance with manufacturers' instructions:

(1) Human immunodeficiency virus, Type 1 (e.g., FDA licensed screening test for anti-HIV-1);

(2) Human immunodeficiency virus, Type 2 (e.g., FDA licensed screening test for anti-HIV-2);

(3) Hepatitis B (e.g., FDA licensed screening test for HBsAg); and

(4) Hepatitis C (e.g., FDA licensed screening test for anti-HCV).

(b) In the case of a neonate, the mother's specimen is acceptable for testing.

(c) Such infectious disease testing shall be performed by a laboratory certified under the Clinical Laboratories Improvement Amendments of 1988 (CLIA).

(d) Human tissue shall be accompanied by records indicating that the donor's specimen has been tested and found negative using FDA licensed screening tests for HIV–1, HIV–2, hepatitis B, and hepatitis C. FDA licensed screening tests labeled for cadaveric specimens must be used when available.

(e) Human tissue for transplantation shall be accompanied by a summary of records or copies of the original records of the donor's relevant medical records as defined in § 1270.3(t) which documents freedom from risk factors for and clinical evidence of hepatitis B, hepatitis C, or HIV infection. There shall be a responsible person designated and identified in the original record and summary of records as having made the determination that the human tissue is suitable for transplantation.

(f) Determination by the responsible person that a donor of human tissue intended for transplantation is suitable shall include ascertainment of the donor's identity, and accurately recorded relevant medical records (as defined in § 1270.3(t)) which documents freedom from risk factors for and clinical evidence of hepatitis B, hepatitis C, and HIV infection.

(g) For corneal tissue procured under legislative consent where a donor medical history screening interview has not occurred, a physical assessment of the donor is required and other available information shall be reviewed. The corneal tissue shall be accompanied by the summary of records documenting that the corneal tissue was determined to be suitable for transplantation in the absence of the donor medical history interview. Corneal tissue procured under legislative consent shall be documented as such in the summary of records.

(h) Human tissue shall be determined to be not suitable for transplantation if from:

(1) A donor whose specimen has tested repeatedly reactive on a screening test for HIV, hepatitis B, or hepatitis C;

(2) A donor where blood loss is known or suspected to have occurred and transfusion/infusion of more than 2,000 milliliters (mL) of blood (i.e., whole blood, reconstituted blood, or red blood cells), or colloids within 48 hours; or more than 2,000 mL of crystalloids within 1 hour; or any combination thereof prior to the collection of a blood specimen from the tissue donor for testing, unless:

(i) A pretransfusion or preinfusion blood specimen from the tissue donor is available for infectious disease testing; or

(ii) An algorithm is utilized that evaluates the volumes administered in the 48 hours prior to collecting the blood specimen from the tissue donor to ensure that there has not been plasma dilution sufficient to affect test results; or

(3) A donor who is 12 years of age or less and has been transfused or infused at all, unless:

(i) A pretransfusion or preinfusion blood specimen from the tissue donor is available for infectious disease testing; or

(ii) An algorithm is utilized that evaluates the volumes administered in the 48 hours prior to collecting the blood specimen from the tissue donor to ensure that there has not been plasma dilution sufficient to affect test results.

Subpart C—Procedures and Records

§ 1270.31 Written procedures.

(a) There shall be written procedures prepared and followed for all significant steps in the infectious disease testing process under § 1270.21 which shall conform to the manufacturers' instructions for use contained in the package inserts for the required tests. These procedures shall be readily available to the personnel in the area where the procedures are performed unless impractical. Any deviation from the written procedures shall be recorded and justified.

(b) There shall be written procedures prepared and followed for all significant steps for obtaining, reviewing, and assessing the relevant medical records of the donor as provided in § 1270.21. Such procedures shall be readily available to personnel who may perform the procedures. Any deviation from the written procedures shall be recorded and justified.

(c) There shall be written procedures prepared and followed for designating and identifying quarantined tissue.

(d) There shall be written procedures prepared, validated, and followed for prevention of infectious disease contamination or cross-contamination by tissue during processing.

(e) In conformity with this section, any facility may use current standard written procedures such as those in a technical manual prepared by another organization, provided the procedures

are consistent with and at least as stringent as the requirements of this part.

§ 1270.33 Records, general requirements.

(a) Records shall be maintained concurrently with the performance of each significant step required in this part in the performance of infectious disease screening and testing of donors of human tissue. All records shall be accurate, indelible, and legible. The records shall identify the person performing the work, the dates of the various entries, and shall be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular tissue involved.

(b) All human tissue shall be quarantined until the following criteria for donor suitability are satisfied:

(1) All infectious disease testing under § 1270.21 has been completed, reviewed by the responsible person, and found to be negative; or

(2) Donor screening has been completed, reviewed by the responsible person, and determined to assure freedom from risk factors for and clinical evidence of HIV infection, hepatitis B, and hepatitis C.

(c) All human tissue processed or shipped prior to determination of donor suitability must be under quarantine, accompanied by records assuring identification of the donor and indicating that the tissue has not been determined to be suitable for transplantation.

(d) All human tissue determined to be suitable for transplantation must be accompanied by a summary of records, or copies of such original records, documenting that all infectious disease testing and screening under § 1270.21 has been completed, reviewed by the responsible person, and found to be negative, and that the tissue has been determined to be suitable for transplantation.

(e) Human tissue shall be quarantined until the tissue is either determined to be suitable for transplantation or appropriate disposition is accomplished.

(f) All persons or establishments that generate records used in determining the suitability of the donor shall retain such records and make them available for authorized inspection or upon request by FDA. The person(s) or establishment(s) making the determination regarding the suitability of the donor shall retain all records, or true copies of such records required under § 1270.21, including all testing and screening records, and shall make them available for authorized inspection or upon request from FDA. Records that can be retrieved from another location by electronic means meet the requirements of this paragraph.

(g) Records required under this part may be retained electronically, or as original paper records, or as true copies such as photocopies, microfiche, or microfilm, in which case suitable reader and photocopying equipment shall be readily available.

(h) Records shall be retained at least 10 years beyond the date of transplantation if known, distribution, disposition, or expiration, of the tissue, whichever is latest.

§ 1270.35 Specific records.

Records shall be maintained that include, but are not limited to:

(a) Documentation of results and interpretation of all required infectious disease tests;

(b) Information on the identity and relevant medical records of the donor, as required by § 1270.21(e) in English or, if in another language translated to English and accompanied by a statement of authenticity by the translator which specifically identifies the translated document;

(c) Documentation of the receipt and/or distribution of human tissue; and

(d) Documentation of the destruction or other disposition of human tissue.

Subpart D—Inspection of Tissue Establishments

§ 1270.41 Inspections.

(a) An establishment covered by these regulations in this part, including any location performing contract services, shall permit an authorized inspector of the Food and Drug Administration (FDA) to make at any reasonable time and in a reasonable manner such inspection of the establishment, its facilities, equipment, processes, products, and records as may be necessary to determine compliance with the provisions of this part. Such inspections may be made with or without notice and will ordinarily be made during regular business hours.

(b) The frequency of inspection will be at the agency's discretion.

(c) The inspector shall call upon a responsible person of the establishment and may question the personnel of the establishment as the inspector deems necessary.

(d) The inspector may review and copy any records required to be kept pursuant to part 1270.

(e) The public disclosure of records containing the name or other positive identification of donors or recipients of human tissue will be handled in accordance with FDA's procedures on disclosure of information as set forth in 21 CFR part 20 of this chapter.

§ 1270.42 Human tissue offered for import.

(a) When human tissue is offered for entry, the importer of record must notify the director of the district of the Food and Drug Administration having jurisdiction over the port of entry through which the tissue is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part.

(b) Human tissue offered for import must be quarantined until the human tissue is released by FDA.

§ 1270.43 Retention, recall, and destruction of human tissue.

(a) Upon a finding that human tissue may be in violation of the regulations in this part, an authorized Food and Drug Administration (FDA) representative may:

(1) Serve upon the person who distributed the tissue a written order that the tissue be recalled and/or destroyed, as appropriate, and upon persons in possession of the tissue that the tissue shall be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or the safety of the tissue is confirmed; and/or

(2) Take possession of and/or destroy the violative tissue.

(b) The written order will ordinarily provide that the human tissue be recalled and/or destroyed within 5 working days from the date of receipt of the order and will state with particularity the facts that justify the order.

(c) After receipt of an order under this part, the person in possession of the human tissue shall not distribute or dispose of the tissue in any manner except to recall and/or destroy the tissue consistent with the provisions of the order, under the supervision of an authorized official of FDA.

(d) In lieu of paragraphs (b) and (c) of this section, other arrangements for assuring the proper disposition of the tissue may be agreed upon by the person receiving the written order and an authorized official of FDA. Such arrangements may include providing FDA with records or other written information that adequately assure that the tissue has been recovered, screened, tested, processed, stored, and distributed in conformance with part 1270.

(e) Within 5 working days of receipt of a written order for retention, recall, and/or destruction of tissue (or within 5 working days of the agency's possession

of such tissue), the recipient of the written order or prior possessor of such tissue shall request a hearing on the matter in accordance with part 16 of this chapter. The order for destruction will be held in abeyance pending resolution of the hearing request.

Dated: July 7, 1997.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97–19819 Filed 7–28–97; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 211

[Docket No. 88N–0320]

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Certain Labeling Controls; Partial Extension of Compliance Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; partial extension of compliance date.

SUMMARY: The Food and Drug Administration (FDA) is announcing a continuation of the partial extension of the compliance date for a provision of the final rule, published in the **Federal Register** of August 3, 1993 (58 FR 41348), revising the packaging and labeling control provisions of the current good manufacturing practice (CGMP) regulations for the use of cut labeling. FDA is extending the date for compliance with a specific provision, as it applies to labeling other than immediate container labels, until the effective date of the regulation finalizing the proposed rule on this subject published elsewhere in this issue of the **Federal Register**.

DATES: The date for compliance with the cut labeling provision at § 211.122(g) (21 CFR 211.122(g)), as it applies to labeling other than immediate container labels, is extended until the effective date of the regulation finalizing the proposed rule on this subject published elsewhere in this issue of the **Federal Register**. The date for compliance with all other provisions of the August 3, 1993, final rule remains August 3, 1994.

FOR FURTHER INFORMATION CONTACT: Thomas C. Kuchenberg, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5621 (Internet electronic mail: kuchenbergt@cder.fda.gov), or Paul J. Motise, Center for Drug Evaluation and Research (HFD–325), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1089 (Internet electronic mail: motise@cder.fda.gov).

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 3, 1993 (58 FR 41348), FDA published a final rule amending the current good manufacturing practice (CGMP) regulations to require that special control procedures be instituted if cut labeling is used in packaging and labeling operations. One of these procedures requires the use of ''appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations'' (§ 211.122(g)(2)). The rule applied to all types of labeling, including product inserts, multiunit containers packaged in individual containers, and shipping containers.

In May 1994, FDA received two citizen petitions from several trade associations requesting that the agency extend the effective date of the rule and reopen the administrative record to receive additional comments on the application of § 211.122(g) to items of labeling other than the immediate container label. The petitions stated that additional time was needed to obtain, install, or validate equipment necessary to comply with the rule. The citizen petitions also asserted that the final rule inappropriately expanded the scope of § 211.122(g) from immediate container labels to all drug product labeling.

In the **Federal Register** of August 2, 1994 (59 FR 39255), FDA extended the compliance date for § 211.122(g) as it applies to labeling other than immediate container labels, and opened the administrative record through October 4, 1994, for comments on the scope of § 211.122(g). All other provisions of the final rule became effective on August 3, 1994. FDA further extended the compliance date to August 2, 1996, in the **Federal Register** of April 28, 1995 (60 FR 20897), and to August 1, 1997, in the **Federal Register** of July 19, 1996 (61 FR 37679).

Elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed rule that would limit the scope of § 211.122(g) to immediate container labels, individual unit cartons, or multiunit cartons when immediate containers are not packaged in individual cartons. The proposed rule would also permit the use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment.

In this final rule, FDA is extending the date for compliance with § 211.122(g), as it applies to labeling other than immediate container labels, until the effective date of the regulation finalizing the proposed rule on this subject published elsewhere in this issue of the **Federal Register**. The date for compliance with all other provisions of the August 3, 1993, final rule remains August 3, 1994.

Dated: July 22, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–19818 Filed 7–28–97; 8:45 am]

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 8726]

RIN 1545–AT95

Requirements for Tax Exempt Section 501(c)(5) Organizations

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final regulations clarifying certain requirements of section 501(c)(5). The requirements are clarified to provide needed guidance to organizations on the requirements an organization must meet in order to be exempt from tax as an organization described in section 501(c)(5).

DATES: These regulations are effective on December 21, 1995.

FOR FURTHER INFORMATION CONTACT: Robin Ehrenberg, (202) 622–6080 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

On December 21, 1995, the IRS published in the **Federal Register** (60 FR 66228) a notice of proposed rulemaking under section 501(c)(5). The proposed regulations clarified that organizations whose principal activity is administering retirement plans are not section 501(c)(5) organizations.