failure of the hydraulic extension system, accomplish the following:

(a) Within 600 flight hours after the effective date of this AD, perform a one-time operational test of the free fall control mechanism of the landing gear to ensure proper release of the MLG for extension by free fall, in accordance with Airbus Industrie All Operator Telex (AOT) 32–14, dated February 3, 1997, or Revision 01, dated March 13, 1997. If any discrepancy is detected in the functioning of the free fall control mechanism of the landing gear, prior to further flight, readjust the mechanism, and repeat the operational test in accordance with the AOT. If any discrepancy is detected in the second operational test, prior to further flight, rerig the free fall control mechanism in accordance with the AOT, and accomplish the actions required by paragraph (b) of this AD.

(b) Within 10 months after the effective date of this AD, perform a functional test of the free fall control mechanism of the landing gear to ensure proper release of the MLG for extension by free fall, in accordance with AOT 32–14, dated February 3, 1997, or Revision 01, dated March 13, 1997. Thereafter, repeat the functional test of the free fall control mechanism of the landing gear at intervals not to exceed 12 months, until the modification required by paragraph (c) of the AD has been accomplished. During any test performed in accordance with paragraph (b) of this AD, if the free fall control mechanism of the landing gear fails to fully extend the MLG, prior to further flight, readjust or rerig the mechanism in accordance with the AOT.

(c) Within 66 months after the effective date of this AD, modify the free fall control mechanism of the landing gear in accordance with Airbus Industrie Service bulletin A300–32–0425, Revision 01 (for Model A300 series airplanes); A310–32–2111, Revision 01 (for Model A310 series airplanes): or A300–32–6072, Revision 01 (for Model A300–600 series airplanes); all dated October 10, 1997; as applicable. Accomplishment of the modification constitutes terminating action for the repetitive functional tests required by paragraph (b) of this AD.

(d) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

(e) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 3: The subject of this AD is addressed in French airworthiness directive 97–113–221(B)R1, dated December 3, 1997.

Issued in Renton, Washington, on May 7, 1998.

John J. Hickey,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 207, 807, and 1271

[Docket No. 97N–484R]

RIN 0910–AB05

Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require manufacturers of certain human cellular and tissue-based products to register with the agency and list their products. In addition, the agency is proposing to amend the registration and listing regulations that currently apply to human cellular and tissue-based products regulated as drugs, devices, and/or biological products. This action is being taken to establish a unified registration and listing program for human cellular and tissue-based products.

DATES: Submit written comments on the proposed rule by August 12, 1998. Submit written comments on the information collection provisions by June 15, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

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

SUPPLEMENTARY INFORMATION:

I. Introduction

FDA is putting in place a comprehensive new system of regulation for human cellular and tissue-based products. As a first step toward accomplishing this goal, the agency is proposing regulations that will require establishments that manufacture those products to register and list their products with the agency.

A. Background

The term ''human cellular and tissue-based products'' encompasses an array of medical products derived from the human body and used for replacement, reproductive, or therapeutic purposes. Skin, tendons, bone, heart valves, and corneas have long been used as replacements for damaged or diseased tissues. Semen, ova, and embryos are transferred for reproductive purposes. Currently, some human cellular and tissue-based products are being developed for new therapeutic uses. For example, scientists are studying the use of manipulated human cells to treat viral infections, Parkinson's disease, and diabetes, among other diseases.

Human cellular and tissue-based products serve a crucial role in medicine, and they have the potential for providing important new therapies. Yet they also raise public health concerns. With the development of new products, and new uses for existing products, come questions about safety and effectiveness that need to be answered through clinical investigation. Furthermore, all human cellular and tissue-based products, because they contain components of the human body, pose some risk of carrying pathogens that could cause disease in health-care personnel, other handlers of tissue, recipients, and family members or other close contacts of recipients.

FDA has never had a single regulatory program for human cellular and tissue-based products. Instead, it has regulated these products on a case-by-case basis responding as it determined appropriate to the particular characteristics of and concerns raised by each type of product. Some tissues have been regulated as medical devices under section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321 *et seq.*). Corneal lenticules, dura mater, heart valve allografts, and umbilical cord vein grafts fall into this category. Other products have been considered biological products under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262) and drugs under the act (hereinafter referred to as biological drugs). Somatic cell therapy products and some gene therapy products fall

into this category. (See 58 FR 53248, October 14, 1993.)

FDA has also relied on section 361 of the PHS Act (42 U.S.C. 264), which provides the authority to issue regulations to prevent the spread of communicable diseases, to regulate tissues that it has chosen not to regulate as devices or biological drugs. In 1993, in response to concerns about the safety of human tissue intended for transplantation, FDA used this authority to require testing and screening of tissue donors for hepatitis and human immunodeficiency viruses. (See 58 FR 65514, December 14,1993.) Until it issued those regulations (''Human Tissues Intended for Transplantation,'' codified in title 21 of the Code of Federal Regulations (CFR) part 1270), FDA exerted little or no regulatory control over certain types of human cellular and tissue-based products. Instead, human tissue for transplantation was subject to some State regulation and to voluntary accreditation systems. Even today, FDA's human tissue regulations do not address the infectious disease risk of donating, processing, and storing reproductive cells and tissue.

FDA has evaluated its approach to regulating human cellular and tissue-based products and has determined that changes are needed. In light of the development of new products, coupled with a growing awareness of infectious-disease concerns, the agency believes that the current patchwork of regulatory policies is no longer adequate and plans to create a comprehensive regulatory program that will cover a broad range of human cellular and tissue-based products. The agency has considered the relevant provisions of the act and the PHS Act and has concluded that these two statutes provide sufficiently broad authority for the proposed regulatory program.

The agency announced its plans for reform in two documents released in February 1997: ''Reinventing the Regulation of Human Tissue,'' and ''A Proposed Approach to the Regulation of Cellular and Tissue-Based Products'' (hereinafter ''Proposed Approach document''). The agency requested written comments on its proposed approach and, on March 17, 1997, held a public meeting to solicit information and views from the interested public. (See 62 FR 9721, March 4, 1997) (Docket No.: 97N–0068). FDA has considered the comments submitted at the public meeting and to the docket in drafting this proposed rule. FDA welcomes comments on the proposed rule from all interested parties.

B. The Proposed Approach

FDA seeks to achieve several goals with its new approach to regulating human cellular and tissue-based products. Primary among them is the improved protection of the public health without the imposition of unnecessary restrictions on research, development, or the availability of new products. Under the new program, the degree of scrutiny afforded different types of products will be commensurate with the risks presented, enabling the agency to use its resources more effectively. Consolidating the regulation of human cellular and tissue-based products into one regulatory program is expected to lead to increased consistency and greater efficiency. Together, these planned improvements should increase the safety of human cellular and tissue-based products, and public confidence in that safety, while encouraging the development of new products.

In developing its proposed approach, FDA examined five issues that it considered fundamental to the proper regulation of the various types of human cellular and tissue-based products. First, the agency asked how the transmission of communicable disease by these products occurs and could be prevented. Second, the agency looked at the types of handling, processing, and manufacturing controls that are necessary to prevent contamination and to preserve the integrity and function of these products. Third, the agency examined concerns about the products' clinical safety and effectiveness. Fourth, FDA considered the type of labeling necessary for proper use of the products and the kind of promotion that would be permissible. Finally, the agency asked how it could best monitor and communicate with the cell and tissue industry.

Through examination of these five public-health and regulatory concerns, FDA was able to develop a proposed comprehensive regulatory scheme tailored to the relevant characteristics of human cellular and tissue-based products. In order to devise an umbrella approach, the agency first focused on the products' common attributes. Then, to ensure appropriate levels of regulation, the agency differentiated between the various types of products based on the public health risks associated with them. For example, the risks posed by cells that are extensively manipulated in a laboratory and then implanted for their systemic effect on a patient are different from those of an unmanipulated tissue that is transplanted into a patient to replace an injured structural tissue.

Taking into account these differences, the agency designed a risk-based tiered approach intended to regulate human cellular and tissue-based products only to the extent necessary to protect public health. Some products will be subject to little or no regulation. For example, no regulatory requirements will be imposed on tissues transplanted into the same patient during the same surgical procedure.

As the potential risk posed by a product increases, so will the level of oversight afforded that product. Thus, minimally processed tissues transplanted from one person to another for their normal structural functions would be subject to infectious disease screening and testing and to requirements for good handling procedures, but would not need FDA premarket review or marketing approval. In contrast, premarket approval would generally be required for cells and tissues that are processed extensively, are combined with noncellular or nontissue components, are labeled or promoted for purposes other than their normal functions, or have a systemic effect. In addition, these products would be subject to requirements for good tissue practices and infectious disease screening and testing, as well as to the good manufacturing practice requirements applicable to drugs and devices.

Although FDA's proposed regulatory approach is far more comprehensive in scope than its present system, some products will not be covered. Among the products not included under the approach are vascularized organs and minimally manipulated bone marrow, both of which fall under the purview of the Health Resources Services Administration. FDA already comprehensively regulates transfusable blood products (e.g., whole blood, red blood cells, platelets, and plasma) under a different regulatory scheme and will not at this time regulate those products as human cellular and tissue-based products. Xenograft transplantation (transplantation using tissues derived from animals) raises different public health issues from transplantation with human tissue, and so will not be subject to the new regulatory program. The new program will also exclude from coverage ancillary products used in cell or tissue propagation, storage, or processing, as well as products that are secreted by or extracted from cells or tissues (e.g., human milk, collagen, urokinase, cytokines, and growth factors), because these products often raise different manufacturing, safety, and effectiveness

issues, and generally are covered by other rules, regulations, or standards.

II. Registration of Human Cellular and Tissue-Based Products

FDA is now proposing to extend registration and listing requirements to manufacturers of human cellular and tissue-based products not currently subject to such requirements.

A. Need for Registration and Listing

In order to implement its new approach to the regulation of human cellular and tissue-based products, FDA needs to be able to assess the state of the cell and tissue industry. Although some human cellular and tissue-based products are currently regulated by the agency as devices or biological drugs—and thus are covered by registration and listing requirements—others have not been subject to such regulation. As a result, FDA does not know the full size and scope of the cell and tissue industry and its products.

Through the current proposal to extend the requirements of registration and product listing to members of the tissue and cell industry not presently under such obligations, FDA seeks to accrue the basic knowledge about the industry that is necessary for its effective regulation. Without reliable data on the tissue and cell industry (e.g., names and addresses of manufacturers and types of products) FDA cannot apply appropriate oversight to a rapidly changing industry. FDA must keep informed of the state of the industry, including developments such as the introduction of new products, in order to understand and respond to all relevant public health issues. Because FDA intends to calibrate its level of regulation to the risks posed by various types of cellular and tissue-based products, it is crucial for the agency to have accurate information about those products.

The proposed registration requirement will facilitate communication between the agency and industry. Once FDA has a complete list of the cell and tissue industry and its products, the agency will be able to reach members of the industry with educational materials and information regarding FDA policies, guidances, and requirements. Important information (e.g., about a newly identified public health risk) can also be quickly disseminated to the industry. Moreover, information obtained through the new registration and listing regulation will permit the agency to monitor the industry more effectively. For example, FDA will be able to identify quickly which establishments should be inspected for compliance with applicable laws and regulations, including those to be issued as part of the new tissue regulation program. Required updating of industry registrations and product lists will ensure that FDA's information about the industry remains current.

B. How Registration Will Be Achieved

In proposing these new registration regulations, FDA seeks to improve the way it collects and manages information about the cell and tissue industry and its products. The agency plans to create a single, comprehensive data base with information about human cellular and tissue-based products, maintained by the Center for Biologics Evaluation and Research (CBER). By requiring registration and product listing from manufacturers not presently subject to such requirements, and by consolidating that new information with data currently being collected, FDA will be able to develop a less fragmented and more efficient oversight program. Meanwhile, manufacturers already under a registration obligation will benefit from the availability of new, electronic procedures.

The main set of regulations being proposed, new part 1271 of title 21 of the CFR, will apply to those human cellular and tissue-based products that the agency will regulate under section 361 of the PHS Act. Proposed part 1271 will cover those products, including products consisting of reproductive cells or tissue, that: (1) Are minimally manipulated; (2) are not promoted or labeled for any use other than a homologous use; (3) have not been combined with or modified by the addition of any noncellular or nontissue component that is a drug or device; and (4) do not have a systemic effect, except in cases of autologous use, transplantation into a first-degree blood relative, or reproductive use. For convenience these products will be referred to as ''products regulated under section 361'' or ''361 products.'' (However, the use of these terms does not indicate that other products will not be regulated under section 361 of the PHS Act. In fact, FDA intends to rely in part on section 361 of the PHS Act when imposing requirements on human cellular and tissue-based products regulated as biological drugs or devices under the act and/or section 351 of the PHS Act.) Examples of products to be regulated under section 361 of the PHS Act include bone, tendons, skin, corneas, and sclera. If all other criteria are met, products with a systemic effect that could come under section 361 of the PHS Act include peripheral and cord blood stem cells used autologously or in first degree blood relatives and sperm, oocytes, and embryos for reproductive use.

Establishments that manufacture human cellular or tissue-based products that meet the criteria set out above would be required to register and list those products under proposed part 1271. However, certain exceptions would apply. For example, although the agency's proposed definition of ''manufacture'' includes distribution, commercial carriers would not need to register. Also, certain scientific, educational, or other uses of cellular or tissue-based products would not be covered by part 1271. These and other exceptions are discussed in greater detail in section III of this document.

In order to unify its registration system, FDA also proposes to amend parts 207 and 807 (21 CFR parts 207 and 807) so that information on human cellular and tissue-based products regulated as biological drugs or devices will be submitted to the same data base used for 361 products. Parts 207 and 807 contain the registration and listing requirements for drugs and devices. Under the proposed amendments, manufacturers of human cellular and tissue-based products regulated as biological drugs or devices will be required to comply with the registration and listing requirements in part 207 or 807, as applicable, by following the procedures set out in proposed part 1271.

Human cellular and tissue-based products subject to regulation as biological drugs or devices are those that do not meet the criteria set out above for regulation under section 361 of the PHS Act. That is, they are: (1) More than minimally manipulated; (2) are promoted or labeled for a nonhomologous use; (3) have been combined with or modified by the addition of a noncellular or nontissue component that is a drug or device; or (4) have a systemic effect (except in cases of autologous use, transplantation into a first degree blood relative, or reproductive use). Examples include: Hematopoietic stem cells intended for use in recipients who are not close blood relatives of the cell donor or for uses other than to reconstitute the cellular components of the blood; more than minimally manipulated bone marrow; hematopoietic stem cells that have been expanded or modified as part of gene therapy; cloned and/or activated lymphocyte therapies for cancer or infectious diseases; bone combined with collagen or growth factors; and manipulated cells for autologous structural use (MAS cells), such as

expanded chondrocytes to repair damaged knee cartilage.

Under the proposed regulatory system, some products that are currently regulated as medical devices might be regulated as section 361 products instead. One such product under consideration is dura mater, the collagenous connective tissue that covers the human brain and spinal cord. Dura mater is excised from cadavers shortly after death, washed, cut into smaller pieces, sterilized, preserved, and reconstituted before use in neurosurgical, gynecological, oral, otolaryngological, and general surgical procedures. This manner of processing does not change the tissue's original characteristics relating to its ability to carry out reconstruction, repair, or replacement and, therefore, would be considered minimal manipulation as defined in proposed part 1271. Moreover, dura mater does not have a systemic effect. Thus, dura mater that is not combined with or modified by the addition of any nontissue or noncellular component that is a drug or device, and that is not promoted or labeled for any use other than a homologous use, appears to meet the proposed criteria in part 1271 for regulation under section 361 of the PHS Act.

Recent reports linking the transmission of Creutzfeldt-Jakob Disease (CJD) to several recipients of human cadaveric dura mater have raised questions as to the controls needed to regulate dura mater. Following discussion of data and information relating to dura mater, on October 6 and 7, 1997, FDA's Transmissible Spongiform Encephalopathy Advisory Committee recommended that FDA adopt measures intended to decrease the risk of CJD transmission via dura mater. These recommendations include specific handling procedures to reduce or eliminate CJD infectious agents in cadaveric dura mater and histological examinations of brain biopsies taken from donor cadavers. In light of these recent developments and the committee's recommendations, FDA is requesting comments on whether FDA's proposal to regulate dura mater under the authority of section 361 of the PHS Act will provide adequate controls, or, conversely, whether tissues with certain risk and disease factors should be subject to premarket submission requirements found in the act and in section 351 of the PHS Act. The agency invites comments regarding the appropriate controls for dura mater and like products, and whether such controls may be appropriately addressed in ''good tissue practice'' requirements specific to these products issued under the authority of section 361 of the PHS Act. In the meantime, FDA will continue to regulate dura mater as a device.

The agency intends to regulate as 361 products human heart valve allografts that meet the criteria of proposed § 1271.10, which are now subject to regulation as medical devices. In the past, these products were considered by FDA to be class III medical devices. In 1994, in a stipulated order of dismissal in *Northwest Tissue Center* v. *Shalala*, No. 91–C–6515 (N.D. Ill., October 7, 1994), FDA stipulated that it would not enforce the class III requirement of premarket approval for human heart valve allografts. In 1995, the American Red Cross (ARC) requested that FDA regulate human heart valve allografts as human tissues for transplantation, rather than as medical devices. ARC's request for jurisdictional change for the regulation of human heart allografts was supported by the Northwest Tissue Center.

The agency now proposes to regulate, as section 361 products, heart valve allografts that are minimally manipulated, do not a have a systemic effect, and are not promoted for a nonhomologous use or combined with a nontissue or noncellular component that is a drug or a device.

C. Legal Authority

FDA is proposing to issue new regulations in part 1271 solely under the authority of section 361 of the PHS Act. Under that section, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (See sec. 1, Reorg. Plan No. 3 of 1966 at 42 U.S.C. 202 for delegation of section 361 authority from the Surgeon General to the Secretary, Health and Human Services; see 21 CFR 5.10(a)(4) for delegation from the Secretary to the Food and Drug Administration.) Intrastate transactions may also be regulated under section 361 of the PHS Act. (See *Louisiana* v. *Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).

Because of their nature as derivatives of the human body, all human cellular and tissue-based products pose a potential risk of transmitting diseases. FDA has determined that it may appropriately and effectively regulate certain of these products (described in section II.B of this document) by controlling the infectious disease risks they present rather than by requiring premarket approval or licensing under the act or the PHS Act.

In order to prevent the spread of infectious disease, FDA must obtain the type of basic information about the industry and its products that these proposed regulations will require be provided to the agency. This information will enable the agency to react swiftly to newly discovered or understood risks by alerting members of the industry of its concerns and, when appropriate, by conducting establishment inspections.

Moreover, the registration regulations now being proposed lay the foundation for a regulatory program that will further the goal of preventing the transmission of communicable disease. FDA intends to propose regulations to be issued at a later date that would require such measures as the maintenance of ''good tissue practices'' and various tests for communicable diseases. Without the information that the agency will collect through establishment registration and product listing, FDA cannot effectively monitor compliance with these future regulations—and, thus, prevent the transmission of communicable disease.

Authority for the enforcement of section 361 of the PHS Act is provided by 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, a fine of not more than $1,000, or both (42 U.S.C. 271(a)). In addition, Federal District Courts have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act. The agency intends, in a future rulemaking, to issue regulations including requirements for testing, good tissue practices, and enforcement under the authority of section 361 of the PHS Act.

Human cellular and tissue-based products that do not meet FDA's criteria set forth in part 1271 for regulation solely under section 361 of the PHS Act are subject to regulation as biological drugs or devices, and their manufacturers are required to register with the agency under section 510 of the act. Regulations implementing section 510 are found under parts 207 and 807, among other parts. As discussed earlier, in order to consolidate its data base on the cell and tissue industry and thus to improve its oversight functions, FDA proposes to amend parts 207 and 807 to require registering establishments to follow the procedures set out in part 1271. Section 510 of the act remains the authority for the substantive registration requirement for products subject to parts 207 and 807. Because harmonizing the registration and listing procedures

applicable to the various human cellular and tissue-based products is intended to further the goal of preventing the spread of communicable disease, the agency is also relying on the additional authority of section 361 of the PHS Act for the proposed amendments to parts 207 and 807.

III. Summary of the Proposed Regulations

A. Purpose, Coverage, and Exceptions of Part 1271

1. Purpose

The purpose of part 1271, as set out in § 1271.1, is to establish a unified registration and product listing system for establishments that manufacture human cellular and tissue-based products.

2. Coverage

Section 1271.1 states that manufacturers of human cellular and tissue-based products regulated under section 361 of the PHS Act are required by part 1271 to register and list their products with CBER. These products are further described in § 1271.10, which states who must register and submit a list. The products are those that: (1) Are minimally manipulated; (2) are not promoted for any use other than homologous use; (3) are not combined with or modified by the addition of any nontissue or noncellular component that is a drug or device; and (4) do not have a systemic effect, except in cases of autologous or family-related allogeneic systemic use or reproductive use. Many of these terms are defined in the definition section of the regulation, § 1271.3.

In addition, § 1271.1 notes that manufacturers of products regulated under section 351 of the PHS Act and/or the act are required to register and list their products following the procedures in subpart B of part 1271.

3. Exceptions

Section 1271.20 sets out exceptions to the provisions of part 1271. These exceptions are for activities that do not raise issues the agency currently believes warrant regulation.

a. The use of human cellular or tissue-based products solely for nonclinical scientific or educational purposes does not trigger the registration or listing requirements. Any use for implantation, transplantation, infusion, or transfer into humans is considered clinical use and would be subject to part 1271.

b. An establishment or person that removes human cellular or tissue-based products from an individual and then implants, transplants, infuses, or transfers those cells or tissues into the same individual is not required to register or list with the agency, so long as the human cellular or tissue-based product is quarantined pending completion of the surgery. For example, a surgeon might remove a saphenous vein from a patient for use in a later coronary bypass in the same patient. Registration and listing would not be required unless the saphenous vein was stored with other cellular or tissue-based products. Storage in the same location as other human cellular or tissue-based products gives rise to concerns about the spread of infectious disease and would be considered beyond the bounds of the exception.

c. Carriers that accept, receive, carry, hold, or deliver human cellular or tissue-based products in the usual course of business are not required to register or list.

d. Establishments that receive human cellular or tissue-based products solely for implantation, transplantation, infusion, or transfer within the same facility do not come under the terms of part 1271. This exception is intended only for end-user establishments, that is, establishments that do not procure, distribute, or otherwise manufacture human cellular or tissue-based products.

B. Definitions

Section 1271.3 contains definitions of many of the terms used in part 1271. Some of the definitions relate to the types of product covered by part 1271, e.g., § 1271.3(d) defines ''homologous use.'' Other definitions are intended to clarify the sorts of activities that will trigger the requirements of part 1271, e.g., § 1271.3(f) defines ''manufacture.''

1. Human Cellular or Tissue-Based Product

A *human cellular or tissue-based product* is defined in § 1271.3(e) as a product containing human cells or tissues, or any cell or tissue-based component of such a product.

The following products are excluded from this definition: Vascularized human organs for transplantation; products that are secreted or extracted from humans, such as milk, collagen, and cell factors; minimally manipulated bone marrow; ancillary products used in the propagation of cells or tissues, and cells, tissues, or organs derived from animals.

Whole blood, blood components, or blood derivative products subject to listing under 21 CFR part 607 are also excluded. Such products include, among others, whole blood, red blood cells, cryoprecipitated AHF, platelets, leukocytes/granulocytes, plasma, blood products for diagnostic use, and blood bank reagents. In contrast, peripheral and cord blood stem cells are not subject to the exception for whole blood, blood components and blood derivative products and therefore are subject to part 1271.

2. Minimal Manipulation

One of the criteria for regulation of a human cellular or tissue-based product under section 361 of the PHS Act and part 1271 is that it be minimally manipulated. *Minimal manipulation* is defined in § 1271.3(g). For structural tissue, minimal manipulation is defined as processing that does not alter the original relevant characteristics of the tissue that relate to the tissue's utility for reconstruction, repair, or replacement. For example, separation of structural tissue into components whose relevant characteristics relating to reconstruction or repair are not altered would be considered minimal manipulation, as would extraction or separation of cells from structural tissue in which the remaining structural tissue's relevant characteristics relating to reconstruction and repair remain unchanged. Other examples of procedures that would be considered minimal manipulation include: Cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; and freezing.

For cells (structural and nonstructural) and nonstructural tissues, minimal manipulation is defined as processing that does not alter the relevant biological characteristics and, thus potentially, the function or integrity of the cells or tissues. For example, FDA considers cell selection (e.g., selection of stem cells from amongst lymphocytes and mature cells of other lineages) to be minimal manipulation.

FDA considers the processing of cells and tissue to be ''more than minimal'' if information does not exist to show that the process meets the definition of minimal manipulation. Examples of manipulation not considered minimal, based on current scientific knowledge, include cell expansion, encapsulation, activation, and genetic modification. FDA recognizes that the subsequent accumulation of clinical data and experience about a particular process may demonstrate that it does not alter the original relevant characteristics of the cells or tissue, and the agency will consider this information in determining whether a procedure should be considered minimal as opposed to more-than-minimal

manipulation. For example , FDA previously considered demineralized bone products (DMB) to be more than minimally manipulated. However, at the March 17, 1997, public meeting, and during a July 11, 1997, meeting between the American Association of Tissue Banks and FDA, the agency was urged to reconsider its position regarding the regulatory status of DMB. After reviewing information provided, the agency believes that the relevant characteristics that relate to DMB's utility for replacement, reconstruction and repair are not altered by processing bone specimens into DMB. Therefore, FDA proposes to regulate DMB under section 361 of the PHS Act provided it is used for homologous function and is not combined with a noncellular or nontissue component that is a drug or device because FDA believes DMB falls within the minimal manipulation definition.

3. Homologous Use

The second criterion for regulation under part 1271 is that a human cellular or tissue-based product not be promoted or labeled for any use other than homologous use. *Homologous use* is defined in § 1271.3(d) as the use of a cellular or tissue-based product for replacement or supplementation of a recipient's cells or tissues. Homologous use of a structural tissue-based product occurs when the tissue is used for the same basic structural function that it fulfills in its native state, in a location where such structural function normally occurs. Basic function of a structural tissue is what the tissue does from a biological/physiological point of view, or is capable of doing when in its native state. For example, the agency considers structural tissue to be used for a homologous function when it is used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Conversely, the agency would consider structural tissue to be performing a nonhomologous function when it is fulfilling a function that is different from the basic function it fulfills in its native state.

Examples of homologous use claims for structural tissues that would fall within the scope of part 1271 include bone allograft obtained from a long bone but labeled for use in a vertebra; skin allograft obtained from the arm but labeled for use as a skin graft on the face; pericardium, a structural membranous covering of the heart, labeled for use as a structural membranous covering for the brain; and heart valves labeled for use as heart valves. An example of a nonhomologous use claim for structural tissue is cartilage labeled for placement under the submucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder into the ureter. The cartilage would be performing a structural function (adding volume to change the angle of the ureter) which is different from the function in its native state (to afford flexibility and provide musculoskeletal support).

According to the definition, homologous use of nonstructural cellular or tissue-based products occurs when the cells or tissues are used to perform the function(s) that they performed in the donor. An example of a homologous use claim would be hematopoietic stem cells labeled for use for hematopoietic reconstitution. An example of a nonhomologous use claim for the same cellular product would be a claim for treatment of adrenal leukodystrophies (congenital metabolic deficiencies).

In determining whether a product comes under part 1271 or is instead required to comply with premarketing requirements, FDA has tentatively decided to focus on whether a cellular or tissue-based product is promoted or labeled by its manufacturer for a nonhomologous use, rather than on the intent of the practitioner who uses the product. Accordingly, the actual use of a cellular or tissue-based product for a nonhomologous function would not trigger premarket review requirements if the product was not labeled or promoted for nonhomologous use. This change from the Proposed Approach document comes in response to industry concerns and is expected to lead to the more efficient use of the agency's resources. The agency specifically requests comments on this new language.

4. Nontissue or Noncellular Component

Products combined with or modified by the addition of any *nontissue or noncellular component that is a drug or device* will not be regulated under part 1271. Because ''nontissue or noncellular component' is self-explanatory, FDA does not consider it necessary to define the term. However, the agency has modified the phrase ''nontissue or noncellular component'' with the words ''that is a drug or device'' in order to clarify that water and buffers would not ordinarily be considered nontissue or noncellular components. In contrast, a product composed of human cells or tissue in combination with a mechanical or synthetic component, such as epithelial cells on a biomatrix to cover burns, would not come under part 1271 and would be regulated under section 351 of the PHS Act and/or the act.

5. Systemic Effect

The final requirement for a product to be regulated under part 1271 is that the product not have a systemic effect. Given that ''systemic'' is a commonly used medical term, FDA is not proposing a regulatory definition of the word. The agency would consider the insertion of pancreatic islet cells, pituitary cells, or stem cells into an individual to have a mainly systemic effect. In contrast, the insertion of replacement bone would not have a mainly systemic effect; the effect would be limited to the immediate area around the insertion. FDA recognizes that some products may have both systemic and structural effects but intends that a product's primary effect be determinative.

Earlier discussions of FDA's regulatory plans, including the Proposed Approach document, used the term ''metabolic function.'' After considering concerns raised by comments on the proposed approach, FDA has decided that ''systemic effect'' more accurately reflects the agency's intended meaning.

6. Autologous, Allogeneic, Family-Related Allogeneic, and Reproductive Uses

Under § 1271.10(d), there are several exceptions to the requirement that a human cellular or tissue-based product not have a systemic effect to be regulated under part 1271. These exceptions are for cases of autologous or family-related allogeneic systemic use and for reproductive use. Thus, products with a systemic effect that are utilized for autologous, family-related allogeneic, or reproductive use and that meet the other criteria set out in § 1271.10 will be regulated under part 1271.

Autologous use is defined in § 1271.3(a) as the implantation, transplantation, infusion, or transfer of a cellular or tissue-based product back into the individual from whom the cells or tissue comprising such product were removed. Several comments on the Proposed Approach document pointed out that the agency had used ''Autologous'' in a confusing manner. With the previous definition, the agency intends to clarify the meaning of the word. In contrast with autologous use, allogeneic use (not defined in this regulation) is the transplantation of cells or tissue obtained from a different individual.

FDA is using the phrase ''family-related'' for situations where the

recipient of cells or tissue is a biological parent, child, or sibling of the donor. Thus, *family-related allogeneic use* is defined in § 1271.3(c) as the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product into a first-degree blood relative of the individual from whom cells or tissue comprising such product were removed. Some comments on the Proposed Approach document have disagreed with FDA's definition of ''family-related,'' arguing that its scope should be made broader to include such relatives as cousins and grandparents. Other comments have argued against an exception for family related allogeneic use, asserting that the family-related allogeneic use of products with a systemic effect should be treated no differently from any other allogeneic use. The agency specifically requests further comment on this issue.

The third situation in which a product with a systemic effect will be regulated under part 1271 is when the product contains human reproductive cells or tissue and is for *reproductive use*. In contrast to other tissues with a systemic effect, transfer of reproductive tissues such as semen and ova pose less risk to the health of the recipient from rejection, graft-versus-host disease, and compatibility. In addition, the failure of a reproductive-tissue product will generally cause lesser health risks to the individual than the failure of other systemic products. FDA has decided that it is not necessary to define ''reproductive use'' in the regulation, because the term is well understood.

7. Transfer

Some of the definitions in § 1271.3 contain the terms implantation, transplantation, and infusion, which FDA believes are generally understood. However, FDA is proposing to define, for the purpose of this part, *transfer*, which may not be as well understood, to mean ''the placement of human reproductive cells or tissues into a human recipient.'' This definition, in § 1271.3(k), reflects the way the term ''transfer'' is used within the reproductive tissue industry.

8. Establishment and Manufacture

Other terms defined in § 1271.3 relate to the manufacturing of human cellular and tissue-based products. An *establishment* is defined as a place of business under one management, at one general physical location that engages in the manufacture of human cellular or tissue-based products. The term includes facilities that engage in contract manufacturing services for a manufacturer. The term also includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cellular or tissue-based products.

Under § 1271.3(f), the term manufacture includes all steps in the recovery, screening, testing, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product. The agency interprets certain terms used in the definition of ''manufacture'' in the following ways. By ''recovery'' FDA means obtaining cells or tissues from a donor that are intended for use in human transplantation, infusion, implantation, or transfer. ''Storage'' would include holding human cells or tissue for future distribution or use. ''Processing'' means any activity, other than recovery, performed on a human cellular or tissue-based product, including preventing contamination and preserving the function and integrity of the product. Processing includes preparation, preservation for storage, removal from storage, and any steps to inactivate and remove adventitious agents. ''Distribution'' includes any conveyance or shipment of human cellular or tissue-based product (including importation and exportation), whether or not such conveyance or shipment is entirely intrastate and whether or not possession of the human cellular or tissue-based product is taken.

Many entities and individuals that would be considered manufacturers under part 1271 because they recover human cells or tissues expressed concerns that they would be subject to registration requirements. FDA anticipates that individuals engaged solely in the procurement or recovery of cells or tissues and under contract to organizations that coordinate procurement or recovery of human cells or tissues will not have to independently register under part 1271. Registration will be the responsibility of the employer or contracting organization, which will also be required under future rulemaking to ensure that its employees, agents, and contractors that engage in the recovery of cells or tissues comply with applicable regulations or procedures regarding the collection, safe handling, and proper shipment of human cells or tissues.

C. Procedures for Registration and Listing

The procedures for complying with proposed part 1271, found in subpart B, are designed to impose only a minimal burden on manufacturers while providing FDA with the basic information needed to underpin its regulatory program. Under § 1271.21(a), registration and listing are required within 5 days after the initiation of an establishment's operations. Registration updates are required annually, by December 31, under § 1271.21(b). Section 1271.21(c) governs the semi-annual updating of product lists. Product lists must be updated with the following information: (1) Each human cellular or tissue-based product introduced by the registrant for distribution that has not been included in any list previously submitted; (2) each human cellular or tissue-based product formerly listed for which distribution has been discontinued; (3) each human cellular or tissue-based product for which a notice of discontinuance was submitted and for which distribution has been resumed; and (4) any material change in any information previously submitted. Product list updates must be submitted each June and December; alternatively, they may be submitted at the time the change occurs. When no changes have occurred since the previously submitted product list, no update is required.

Section 1271.22 requires registration, listing, and annual updates to be submitted on Form FDA 3356. That section also tells how to obtain the form and where to submit it, including information on obtaining the form electronically. The agency anticipates that some firms may prefer the ease of obtaining the registration and listing form electronically. For this reason, an electronic version of this form is currently being developed. It will be available by the time the final regulations go into effect.

Section 1271.25 sets out the information required for registration and listing, including the name and address of the establishment. Information required for product listings includes the established and proprietary names of each product, as well as a statement of whether the product meets the criteria set out in § 1271.10. (Any change in whether a product meets these criteria will be considered a ''material change'' subject to reporting under § 1271.21(c)(iv).)

Under § 1271.26, changes in an establishment's ownership or location are to be submitted as an amendment to registration within 5 days of such changes. Section 1271.27 states that the agency will provide the registrant with a permanent registration number. Section 1271.37 sets out the registration and product listing information that will be made available to the public.

At this time, the agency is not proposing to charge a fee for registration

or product listing. FDA is evaluating its authority to assess a fee and the impacts of such a fee. If it determines that a fee it is appropriate, the agency will make such a proposal in a future rulemaking.

D. Amendments to Parts 207 and 807

FDA proposes to add new paragraph (f) to § 207.20 and new paragraph (e) to § 807.20. These additions will state that owners and operators of establishments that recover, screen, test, process, store, label, package, or distribute human cellular or tissue-based products, as defined in § 1271.3(f), shall register and list those products with CBER on Form FDA 3356, following the procedures found in subpart B of part 1271. Thus, instead of following the procedures in subpart C of part 207 (e.g., procedures contained in §§ 207.21, 207.22, 207.25, 207.26, and 207.30), establishments that manufacture human cellular or tissue-based products regulated as biological drugs under the act and the PHS Act would follow the procedures set out in part 1271, subpart B. Regulations that do not pertain to the procedural requirements for registration and listing (e.g., § 207.39, on misbranding) would still apply. In addition, new § 207.20(f) will specifically state that the procedures for submitting additional information, in § 207.31, remain applicable.

With respect to human cellular or tissue-based products regulated as devices under the act, manufacturers would follow the registration and listing procedures of part 1271, subpart B, instead of those found in part 807, subpart B (e.g., procedures in §§ 807.21, 807.22, 807.25, 807.26, and 807.30). As would be the case for devices, the requirements for additional listing information in § 807.31 will remain in place and regulations that do not pertain to registration and listing (e.g., § 807.39) would still be applicable.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).

The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation) in any 1 year. The agency has determined that the proposed rule is a significant rule as described in the Executive Order, but not a significant action as defined in the Unfunded Mandates Reform Act. Aggregate impacts of the rule, and aggregate expenditures caused by the rule, will not approach $100 million for either the public or the private sector.

An analysis of available information suggests that costs to the entities most affected by this rule, including small entities, are not expected be significant, as described in the analysis below. Therefore, the agency certifies that this rule will not have a significant impact on a substantial number of small entities.

A. Objective and Basis of the Proposed Action.

FDA is proposing this action as a first step in the regulation of the rapidly evolving industry of human cellular and tissue-based products. This industry has not been previously subject to a comprehensive regulatory program by FDA or other public health authorities. Lack of a single regulatory approach or registration system has prevented the agency from acquiring information regarding the full size of the cell and tissue industry and the scope of its products. The proposed rule will require all manufacturers of human cellular and tissue-based products to register with the agency and to submit to the agency a list of their products. Through registration and listing, FDA will be able to identify industry participants and the products manufactured. This will enable the agency to more efficiently monitor the industry, distribute new information such as guidances, policies, or requirements, and identify entities that may be subject to inspection by FDA. This action is taken solely under the authority of section 361 of the PHS Act. Section 361 is also used as authority to amend parts 207 and 807 so that the registration data bases developed for drugs and devices may be consolidated with the data base of the proposed human cell and tissue registration program. Section 510 of the act remains the substantive registration requirement for products subject to parts 207 and 807. FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

B. Small Entities Affected

This proposal affects both entities that currently register with FDA and submit product lists to the agency under applicable sections of the act (parts 207 and 807), and those entities that are not presently required to register or list with the agency. FDA has structured registration and listing to have a minimal impact on affected entities. However, the agency anticipates that the impact will be greater for those entities that do not currently register or list.

The number of entities that will be required to begin registration and listing under part 1271 is difficult to ascertain. Because the agency has not previously regulated certain human cellular and tissue-based products, the agency can only approximate the number of entities that may fall under the requirements of the proposed rule. This lack of accessible, accurate information is, in fact, a major reason behind the agency's registration and listing initiative. In calculating the burden, the agency has used information obtained from various trade organizations related to the human cellular and tissue-based industry. Several organizations also provided estimates of what portion of the industry their membership represented, and the agency included in its analysis the 65 manufacturers of human cellular and tissue-based device products that are registered with the agency under part 807. The Musculoskeletal Transplant Foundation lists approximately 25 tissue and organ recovery members, which it estimates to be about one-third of the tissue and organ procurement organizations in the United States. The National Bone Marrow Donor Program, which includes establishments that recover peripheral blood stem cells, lists approximately 101 donor centers and 114 collection centers in the United States. The American Association of Tissue Banks (AATB) lists approximately 60 tissue banks. The Eye Bank Association of America represents about 112 eye banks, which it estimates is about 95 percent of the U.S. eye banks. The American Society for Reproductive Medicine has a membership of approximately 7,200 physicians, researchers, and other health care professionals, of which perhaps only 120 are fertility doctors who would be subject to the registration and listing requirements. In addition, it is estimated that there are about 90 semen

depositories in commercial operation. Any of the entities described above that engage in manufacture (including, but not limited to, recovery, screening, testing, processing, storage, labeling, packaging, or distribution) of human cellular or tissue-based products would be affected by the proposed rule. A great majority of these approximately 680 entities would be considered ''small'' under criteria established by the Small Business Administration. FDA invites comments on this analysis of the number of entities that may be affected by the proposed registration and listing rule.

C. Nature of the Impact

The main cost involved in implementing the proposed rule would be the time required to obtain the form, read the instructions, and complete and submit the form. FDA has no precise estimate of the initial registration and listing procedure but estimates that it should require an average of 1 hour of staff time per registrant. This estimate is supported by the estimates prepared for the completion of the blood product registration on FDA Form 2830, which is similar in length, type of information requested, and complexity to the proposed Form FDA 3356 (62 FR 11898, March 13, 1997). In addition, the proposed rule will require an update of the product list which is estimated to require about 0.5 hour of staff time. Thus, registration and listing is anticipated to require about 1.5 hours of staff time per annum. At an estimated $38.00/hour value of staff time, most registrants are expected to incur an annual cost of approximately $57.00 to comply with the requirements of the proposed rule. There are no specific educational or technical skills required to complete and submit the registration and listing form. Similar activities are generally completed by trained and qualified employees of an establishment who are intimately involved with the operations of the entity.

The proposed rule is the first step in creating a tiered, risk-based regulatory scheme that will tailor the degree of scrutiny afforded to different products to the risks associated with each product. Through registration and listing, FDA will acquire the information needed to characterize the nature and extent of the human cellular and tissue-based industry. This information will enable FDA to efficiently and effectively respond to emerging public health concerns related to human cellular or tissue-based products. Lists of industry members and their products will also help FDA disseminate educational materials and other important information regarding FDA policies, guidances, and requirements.

D. Minimizing the Impact on Small Entities

FDA recognizes that a large number of the establishments that would be required to register and list under the proposed rule will be small entities with limited resources. In recognition of this, the agency is proposing that the information to be provided during registration and listing be only that which is necessary to achieve the agency's goals of industry characterization and identification of its participants. To alleviate the impact on entities, especially small entities, FDA proposes that Form FDA 3356 be electronically retrievable. Future development of registration and listing will consider the use of electronic submissions (e-mail or Internet) and electronic signatures.

V. Proposed Effective Date

The agency proposes that any final rule that may issue based on this proposed rule become effective 180 days after its date of publication in the **Federal Register**.

VI. Environmental Impact

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

VII. The Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, gathering necessary information, and completing and reviewing the report.

With respect to the following collection of information, FDA 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.

Title: Establishment Registration and Product Listing for Manufacturers of Human Cellular and Tissue-based Products.

Description: FDA is proposing to require establishments that recover, screen, test, process, store, label, package, or distribute any human cellular or tissue-based product to register with FDA and submit lists of the manufactured products to be updated twice a year. FDA proposes to define certain terms relevant to registration and listing, define which manufactures will be subject to the provisions of the proposed rule, and provide a form (Form FDA 3356) to be used for the entry of an entity's name and location information and its product list. FDA is proposing this action in response to the agency's public health concerns regarding products comprised of human cells or tissues, or that incorporate such cells or tissues. Through this initiative the agency will improve its ability to protect the public health by controlling the spread of communicable diseases.

Description of Respondents: Manufacturers of human cellular and tissue-based products.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR	Form No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response (average)	Total Hours
1271	FDA 3356	680	2	1,360	0.75	1,020
207.20	FDA 3356	1	2	2	0.75	1.5

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

21 CFR	Form No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response (average)	Total Hours
807.20	FDA 3356	65	2	130	0.75	97.5
TOTAL		746	2	1,492	0.75	1,119

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

Because many manufacturers of products using human cells or tissues have not been required to register or list with FDA, the agency's ability to predict how many entities would be affected by the proposed rule is limited. The estimates for number of respondents are based on the number of entities currently registered with FDA as manufacturers of human cellular or tissue-based devices, membership information obtained from trade organizations related to the manufacturing of products utilizing human cells or tissues, and an estimate of entities that are not presently registered with FDA or members of trade organizations but that would be subject to registration under the proposed rule. The annual frequency of responses is based on the requirement in the proposed rule for the submission of an annual registration and a biannual product list updating. In practice, it is expected that the annual registration, or annual confirmation of registration for entities that have already registered once, and the first product list update of the biannual requirement will be completed simultaneously on the same form. The hours for response was obtained by averaging the estimates of 1 hour of staff time for the initial, or confirmatory registration and 0.5 hour of staff time for the update of the product list. The ''Total Hours'' column provides the estimated total number of hours for registration and listing by manufacturers of human cellular and tissue-based products under proposed part 1271, existing §§ 207.20 and 807.20 as they would be amended by the proposal, and a cumulative total for registration and listing by manufacturers of such products under all three sections.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for review of the information collection provisions. Interested persons are requested to submit written comments regarding information collection by June 15, 1998, to the Office of Information and Regulatory Affairs, OMB (address above), Attention: Desk Officer for FDA.

VIII. Request for Comments

Interested person may, on or before August 12, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal, except that comments regarding information collection provisions should be submitted in accordance with the instructions in section VII of this document. Two copies of any comments on issues other than information collection are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 207

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 807

Confidential business information, Imports, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 1271

Human cellular and tissue-based products, Reporting and recordkeeping requirements.

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

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

1. The authority citation for 21 CFR part 207 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 356, 357, 360, 360b, 371, 374; 42 U.S.C. 262, 264, 271.

2. Section 207.20 is amended by adding new paragraph (f) to read as follows:

§ 207.20 Who must register and submit a drug list.

* * * * *

(f) Owners and operators of establishments or persons engaged in the recovery, screening, testing, processing, storage, or distribution of human cellular or tissue-based products, as defined in § 1271.3(e) of this chapter, that are regulated under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act shall register and list those products with the Center for Biologics Evaluation and Research on Form FDA 3356 following the procedures set out in subpart B of part 1271 of this chapter, except that the additional listing information requirements in § 207.31 remain applicable.

PART 807—ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR MANUFACTURERS AND DISTRIBUTORS OF DEVICES

3. The authority citation for 21 CFR part 807 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 360, 360c, 360e, 360i, 360j, 371, 374; 42 U.S.C. 264, 271.

4. Section 807.20 is amended by adding new paragraph (e) to read as follows:

§ 807.20 Who must register and submit a device list.

* * * * *

(e) Owners and operators of establishments or persons engaged in the recovery, screening, testing, processing, storage, or distribution of human cellular or tissue-based products, as defined in § 1271.3(e) of this chapter, that are regulated under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act shall register and list those products with the Center for Biologics Evaluation and Research on Form FDA 3356 following the procedures set out in subpart B of part 1271 of this chapter, except that the additional listing information requirements in § 807.31 remain applicable.

5. New part 1271 is added to read as follows:

PART 1271—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN CELLULAR AND TISSUE-BASED PRODUCTS

Subpart A—General Provisions

Sec.

Subpart B—Procedures for Registration and Listing

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

Subpart A—General Provisions

§ 1271.1 Purpose.

The purpose of this part is to create a unified registration and product listing system for establishments that manufacture human cellular and tissue-based products. Manufacturers of human cellular and tissue-based products regulated under the authority of section 361 of the Public Health Service Act are required by this part to register and list their products with the Food and Drug Administration, Center for Biologics Evaluation and Research. Under §§ 207.20(f) and 807.20(e) of this chapter, manufacturers of human cellular and tissue-based products regulated under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act are required to register and list their products following the procedures in subpart B of this part.

§ 1271.3 Definitions.

The following definitions apply only to this part:

(a) *Autologous* use means the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product back into the individual from whom the cells or tissue comprising such product were removed.

(b) *Establishment* means a place of business under one management, at one general physical location, that engages in the manufacture of human cellular or tissue-based products. The term includes, among others, facilities that engage in contract manufacturing services for a manufacturer of human cellular or tissue-based products. The term also includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cellular or tissue-based products, except that an individual engaged solely in the procurement or recovery of cells or tissues or under contract to a registered establishment is not required to independently register.

(c) *Family-related allogeneic use* means the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product into a first-degree blood relative of the individual from whom cells or tissue comprising such product were removed.

(d) *Homologous use* means the use of a cellular or tissue-based product for replacement or supplementation and:

(1) For structural tissue-based products, occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs; or

(2) For cellular and nonstructural tissue-based products, occurs when the cells or tissue is used to perform the function(s) that they perform in the donor.

(e) *Human cellular or tissue-based product* means a product containing human cells or tissues or any cell or tissue-based component of such a product. The following products are not considered human cellular or tissue-based products and establishments that manufacture only one or more of the following would not be subject to the registration or listing provisions of this part:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under part 607 of this chapter;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors;

(4) Minimally manipulated bone marrow;

(5) Ancillary products used in the propagation of cells or tissues; or

(6) Cells, tissues or organs derived from animals.

(f) *Manufacture* means, but is not limited to, any or all steps in the recovery, screening, testing, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product.

(g) *Minimal manipulation* means:

(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

(2) For cells and nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

(h) *Transfer* means the placement of human reproductive cells or tissues into a human recipient.

§ 1271.10 Who must register and submit a list.

All owners and operators of establishments, both foreign and domestic, that manufacture human cellular and tissue-based products, whether or not the product enters into interstate commerce, are required under this part to register with the Food and Drug Administration and submit to the agency a list of each human cellular or tissue-based product manufactured, if such product is:

(a) Minimally manipulated;

(b) Not promoted or labeled for any use other than a homologous use;

(c) Not combined with or modified by the addition of any nontissue or noncellular component that is a drug or a device; and

(d) Does not have a systemic effect; except that a human cellular or tissue-based product that meets the requirements in paragraphs (a), (b), and (c) of this section may have a systemic effect if the product is for:

(1) Autologous use;

(2) Family-related allogeneic use; or

(3) Reproductive use and contains human reproductive cells or tissue.

§ 1271.20 Establishments not required to register or list under this part.

The following establishments are not required to register or submit product listings under this part:

(a) Establishments that use human cellular or tissue-based products solely for nonclinical scientific or educational purposes;

(b) Establishments that remove human cellular or tissue-based products from an individual and implant such cells or tissues into the same individual during the same surgical procedure;

(c) Carriers who accept, receive, carry, hold, or deliver human cellular or tissue-based products in the usual course of business as carriers; and

(d) Establishments that only receive or store human cellular or tissue-based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility.

Subpart B—Procedures for Registration and Listing

§ 1271.21 When to register and list.

(a) Owners and operators of establishments required to register and list under § 1271.10 or required under other provisions of this chapter to follow the procedures in subpart B of this part shall register within 5 days after beginning operations and shall submit a list of every product that is manufactured.

(b) Owners and operators of establishments shall update their registration annually by December 31, except as required by § 1271.26. Annual registration may be accomplished in conjunction with the updating of product lists under paragraph (c) of this section.

(c)(1) Owners and operators of establishments shall update their product lists during each June and December or, at their discretion, at the time the change occurs, with the following information:

(i) A list of each human cellular or tissue-based product introduced by the registrant for distribution that has not been included in any list previously submitted. The registrant shall provide all of the information required by § 1271.25(b) for each such product.

(ii) A list of each human cellular or tissue-based product formerly listed in accordance with paragraph (a) of this section and for which distribution has been discontinued, including for each product so listed, the identity by established name and proprietary name, and the date of discontinuance. It is requested but not required that the reason for discontinuance of distribution be included with this information.

(iii) A list of each human cellular or tissue-based product for which a notice of discontinuance was submitted under paragraph (c)(1)(ii) of this section and for which distribution has been resumed, including the identity by established name and proprietary name, the date of resumption, and any other information required by § 1271.25(b) not previously submitted.

(iv) Any material change in any information previously submitted. Material changes include any change in whether the product meets the criteria set out in § 1271.10.

(2) When no changes have occurred since the previously submitted list, no report is required.

§ 1271.22 How and where to register and list.

(a) Establishment registration, product listing, and updates of registration and listing shall be submitted on Form FDA 3356 to the Center for Biologics Evaluation and Research (HFM–370), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, Attention: Tissue Establishment Registration Coordinator, or electronically in accordance with instructions provided with Form FDA 3356.

(b) Copies of Form FDA 3356 can be obtained from the Center for Biologics Evaluation and Research (HFM–370), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, Attention: Tissue Establishment Registration Coordinator (from any Food and Drug Administration district office); by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by calling the Fax Information System at 1–888–CBER–FAX or 301–827–3844. Persons with access to the Internet may obtain the document using the World Wide Web (WWW) by connecting to: CBER at ''http//www.fda.gov/cber/publication.htm''.

§ 1271.25 Information required for registration and listing.

(a) Registration shall include:

(1) The legal name(s) of the establishment;

(2) Each location, including the street address of the establishment and the postal service zip code;

(3) The name, address, and title of the reporting official; and

(4) A signed and dated statement by the reporting official affirming that all information contained in the registration and listing form is true and accurate.

(b) Listing information shall include all human cellular or tissue-based products (including the established name and the proprietary name) that are recovered, screened, tested, processed, stored, labeled, packaged, and distributed. Listing information shall also include a statement of whether each product meets the criteria set out in § 1271.10.

(c) Copies of all contract service agreements shall be available at the time of inspection of the establishment.

§ 1271.26 Amendments to registration.

Changes in the ownership or location of an establishment shall be submitted as an amendment to registration within 5 days of such changes.

§ 1271.27 Assignment of a registration number.

(a) A permanent registration number will be assigned to each location.

(b) FDA acceptance of establishment registration and listing forms for human cellular and tissue-based products does not constitute a determination that an establishment is in compliance with applicable rules and regulations.

§ 1271.37 Inspection of establishment registration and product lists.

(a) A copy of the Form FDA 3356 filed by each establishment will be available for inspection at the Office of Communication, Training, and Manufacturers Assistance (HFM–48), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. In addition, there will be available for inspection at each of the Food and Drug Administration district offices the same information for firms within the geographical area of such district office. Upon request and receipt of a self-addressed stamped envelope, verification of a registration number or the location of a registered establishment will be provided. The following information submitted under the human cellular and tissue-based product requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(1) A list of all human cellular and tissue-based products;

(2) A list of all human cellular and tissue-based products manufactured by each establishment;

(3) A list of all human cellular and tissue-based products discontinued; and

(4) All data or information that has already become a matter of public record.

(b) Requests for information regarding human cellular and tissue-based product establishment registrations and product listings should be directed to the Office of Communication, Training and Manufacturers Assistance (HFM–48), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

Dated: March 10, 1998.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

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