involved in nuclear, missile, or military activities included in Supplement No. 4 to part 744 (Entity List). All license applications for exports and reexports to India and Pakistan not meeting these criteria for presumption of denial will be considered on a case-by-case basis under other licensing policies set forth in the EAR applicable to such computers.

(iv) *Post-shipment verification.* This section outlines special post-shipment reporting requirements for exporters of certain computers to destinations in Computer Tier 3. Post-shipment reports must be submitted in accordance with the provisions of this paragraph (b)(3)(iv), and all relevant records of such exports must be kept in accordance with part 762 of the EAR.

(A) Exporters must file post-shipment reports for computer exports, as well as exports of items used to enhance previously exported or reexported computers, according to the following schedule:

(*1*) For exports occurring prior to February 26, 2001, where the CTP is greater than 12,500 MTOPS;

(*2*) For exports on or after February 26, 2001, but before March 20, 2001 where the CTP is greater than 28,000 MTOPS; and

(*3*) For exports on or after March 20, 2001 where the CTP is greater than 85,000 MTOPS.

(B) *Information that must be included in each post-shipment report.* No later than the last day of the month following the month in which the export takes place, the exporter must submit the following information to BXA at the address listed in paragraph (b)(3)(iv)(C) of this section:

(*1*) Exporter name, address, and telephone number;

(*2*) License number;

(*3*) Date of export;

(*4*) End-user name, point of contact, address, telephone number;

(*5*) Carrier;

(*6*) Air waybill or bill of lading number;

(*7*) Commodity description, quantities—listed by model numbers, serial numbers, and CTP level in MTOPS; and

(*8*) Certification line for exporters to sign and date. The exporter must certify that the information contained in the report is accurate to the best of his or her knowledge.

(C) *Mailing address.* A copy of the post-shipment report[s] required under paragraph (b)(3)(iv)(A) of this section shall be delivered to one of the following addresses. Note that BXA will not accept reports sent C.O.D.

(*1*) For deliveries by U.S. postal service: U.S. Department of Commerce, Bureau of Export Administration, P.O. Box 273, Washington, D.C. 20044, Attn: Office of Enforcement Analysis HPC Team, Room 4065.

(*2*) For courier deliveries: U.S. Department of Commerce, Office of Enforcement Analysis HPC Team, 14th Street and Constitution Ave., NW, Room 4065, Washington, DC 20230.

* * * * *

PART 748—[AMENDED]

6. Section 748.10 is amended by revising paragraph (b)(3) as follows:

§ 748.10 Import and end-user certificates.

* * * * *

(b) * * *

(3) Your transaction involves an export to the People's Republic of China (PRC) of a computer. You must obtain a PRC End-User Certificate, regardless of dollar value, as follows:

(i) For exports of computers as described by § 740.7(d)(2) of the EAR, regardless of value, to the People's Republic of China. (See paragraph (c) of this section for information on obtaining the PRC End-User Certificate.) Exporters are required to obtain a PRC End-User Certificate before exporting computers to the PRC. In addition, exporters are required to provide the PRC End-User Certificate Number to BXA as part of their post-shipment report (see § 740.7(d)(5)(v) of the EAR). When providing the PRC End-User Certificate Number to BXA, you must identify the transaction in the post shipment report to which that PRC End-User Certificate Number applies. The original PRC End-User Certificate shall be retained in the exporter's files in accordance with the recordkeeping provisions of § 762.2 of the EAR.

(ii) For exports of computers that require license applications.

* * * * *

Dated: January 16, 2001.

Matthew S. Borman,

Acting Deputy Assistant Secretary for Export Administration.

[FR Doc. 01–1623 Filed 1–16–01; 4:49 pm]

BILLING CODE 3510–33–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 207, 807, and 1271

[Docket No. 97N–484R]

Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to require human cells, tissue, and cellular and tissue-based product establishments to register with the agency and list their human cells, tissues, and cellular and tissue-based products. FDA is also amending the registration and listing regulations that currently apply to human cells, tissues, and cellular and tissue-based products regulated as drugs, devices, and/or biological products. These actions are being taken to establish a unified registration and listing program for human cells, tissues, and cellular and tissue-based products.

DATES: The regulation is effective April 4, 2001, except for 21 CFR 207.20(f), 807.20(d), and 1271.3(d)(2), which are effective on January 21, 2003.

FOR FURTHER INFORMATION CONTACT: Valerie A. Butler, 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

We, FDA, are putting in place a comprehensive new system of regulation for human cells, tissues, and cellular and tissue-based products. The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products. Under the new system, the regulation of different types of human cells, tissues, and cellular and tissue-based products will be commensurate with the public health risks presented, enabling us to use our resources more effectively. Consolidating the regulation of human cells, tissues, and cellular and tissue-based products into one regulatory program is expected to lead to increased consistency and greater efficiency. Together, these planned improvements will increase the safety of human cells,

tissues, and cellular and tissue-based products, and public confidence in their safety, while encouraging the development of new products.

A. Background

In 1997, we announced our regulatory plans for human cells, tissues, and cellular and tissue-based products in two documents:

- ''A Proposed Approach to the Regulation of Cellular and Tissue-Based Products'' (62 FR 9721, March 4, 1997) and
- ''Reinventing the Regulation of Human Tissue'' (Ref. 1).

The proposed approach described a comprehensive plan for regulating human cells, tissues, and cellular and tissue-based products that would include establishment registration and product listing, donor-suitability requirements, good tissue practice regulations, and other requirements. Under this tiered, risk-based approach, we proposed to exert only the type of government regulation necessary to protect the public health. To accomplish this goal, we planned to issue new regulations under the communicable disease provisions of the Public Health Service Act (the PHS Act). Some human cellular and tissue-based products would be regulated only under these new regulations, while other human cellular and tissue-based products would also be regulated as drugs, devices, and/or biological drugs. We requested written comments on the proposed approach and, on March 17, 1997, held a public meeting (62 FR 9721).

Since 1997, we have published three proposed rules to implement the proposed approach. In 1998, as a first step toward accomplishing these goals, we published the proposed rule, ''Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products'' (63 FR 26744, May 14, 1998) (the ''registration proposed rule''). That rule proposed to require cell and tissue establishments to register with us and submit a list of their human cellular and tissue-based products. We also proposed modifications to current registration and listing requirements for drugs and devices under which cell and tissue establishments already regulated under the Federal Food, Drug, and Cosmetic Act (the act) and/or section 351 of the PHS Act (42 U.S.C 262) would register and list following the new procedures.

In addition to the registration proposed rule, we published two more proposed rules:

- Suitability Determination for Donors of Human Cellular and Tissue-Based Products (64 FR 52696, September 30, 1999) (the ''donor-suitability proposed rule''); and
- Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (66 FR 1508, January 8, 2000) (the ''GTP proposed rule''). Together, these three rules when finalized would establish a comprehensive regulatory program for human cellular and tissue-based products, to be contained in part 1271 (21 CFR part 1271).

In the three proposed rules, we used the term ''human cellular and tissue-based products.'' In this final rule, we have changed the term to ''human cells, tissues, and cellular and tissue-based products'' (abbreviated ''HCT/P's''). This change in terminology is a clarification and does not affect the scope of the definition, which continues to encompass an array of articles containing or consisting of human cells or tissues, and intended for implantation, transplantation, infusion, or transfer into human recipients, including investigational products. The definition of ''human cells, tissues, or cellular or tissue-based product'' is intended to cover HCT/P's at all stages of their manufacture, from recovery through distribution. Some examples of HCT/P's include skin, tendons, bone, heart valves, corneas, hematopoietic stem cells, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

B. Implementation of the New Regulations

We had intended to finalize the registration proposed rule with the two other rules that would make up part 1271 in its entirety, and to implement all three rules together. However, we are now making the registration rule final, with staggered effective dates, before finalizing the two remaining portions of part 1271. We are taking this action because of recent concerns raised about the safety of tissue, which have led us to believe that accelerating the collection of basic information about the rapidly growing tissue industry is vital. This medical sector has grown rapidly, with a need for clearer standards and improved accountability. The Department of Health and Human Services met in mid-2000 with representatives of key tissue-related organizations, who supported finalization of this regulation as quickly as possible, instead of awaiting simultaneous publication with the other tissue regulations. For these reasons, we are going to begin collecting registration and listing information, while continuing to develop the remainder of the final rules that will complete part 1271, and we have changed the effective date of this rule from the proposed 180 days to 75 days after the date of publication in the **Federal Register**. As part of completing the rulemaking for part 1271, we would make any necessary conforming amendments to this regulation to make it consistent with any changes made in the remainder of the rulemaking process, and we would revoke part 1270.

Establishments that engage in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation currently regulated under section 361 of the PHS Act (42 U.S.C. 264) and the regulations in part 1270 (21 CFR part 1270) (''Human Tissue Intended for Transplantation'') will be required to begin registering with the agency and listing their HCT/P's within 30 days after the effective date of this final rule. The effective date for all other human cells, tissues, and cellular and tissue-based products (as described in § 1271.3(d)(2)) is 2 years after publication, by which time we expect to have completed rulemaking for all the subparts of part 1271. (Some establishments that are not required to register and list until the second effective date have expressed a desire to submit registration and listing forms as soon as possible. In response, FDA is prepared to accept registration and listing forms submitted in advance of the second effective date. However, FDA is not soliciting this information.) Once the entire rulemaking is complete, the new regulatory approach would apply to a broad range of human cells, tissues, and cellular and tissue-based products, including reproductive cells and tissue; hematopoietic stem cells; and tissues and cells regulated as devices, drugs, and/or biological products.

Staggering the effective dates of this regulation permits us to begin collecting important registration and listing information soon from those establishments currently regulated under part 1270, while continuing to proceed through rulemaking to develop the remainder of part 1271. We believe that this action may prevent an unintentional gap in the regulation of certain currently regulated HCT/P's, permit an orderly implementation process, and avoid duplicative information collection. If we instead implemented the regulation immediately for all HCT/P's, this action could have the effect of shifting the regulation of certain products (e.g., HCT/P's currently regulated as devices

that meet the criteria set out in § 1271.10 for regulation solely under section 361 of the PHS Act) into the new regulatory system before standards and enforcement provisions are in place. Staggering the effective dates also helps permit an orderly implementation process. Establishments that manufacture cells and tissues that will be regulated for the first time under new part 1271 may require more time than those currently regulated to implement the provisions of this final rule. However, we also recognize that unanticipated delays in completing the rulemaking for the remainder of part 1271 could occur. Should the rulemaking proceedings be delayed past the 2-year timeframe, we will consider whether to maintain the 2-year effective date for the HCT/P's described in § 1271.3(d)(2) or whether to extend that date for some or all of those HCT/P's.

C. Legal Authority

We are issuing this final rule under the authority of section 361 of the PHS Act. Under section 361 of the PHS Act, we may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (See sec. 1, Reorg. Plan No. 3 of 1966 at 42 U.S.C. 202 for delegation of section 361 of the PHS Act 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 FDA.) 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).)

HCT/P's are derivatives of the human body and thus pose a potential risk of transmitting infectious disease. We have determined that some HCT/P's may be effectively regulated solely by controlling the infectious disease risks they present. The regulation now being finalized forms the foundation for a regulatory program that will further the goal of preventing the transmission of communicable disease. To begin implementing this regulatory program, we are publishing the registration final rule, with staggered effective dates so that those HCT/P establishments not currently subject to regulation under section 361 of the PHS Act will have adequate preparation time and FDA can continue working towards finalizing the remainder of the program.

For this regulatory system to be effective in preventing the spread of disease, we must obtain basic information about the human cell and tissue industry and its HCT/P's. The information to be submitted in compliance with the registration and listing requirements in subpart B will provide baseline data on establishments that will be subject to part 1271. This information from the registration rule will assist us in reacting swiftly to newly discovered or understood risks by alerting members of the industry to our concerns and, when appropriate, by conducting establishment inspections. Without this information, we would not be able to effectively monitor compliance with the proposed donor-suitability, GTP, and other regulations that make up the rest of the regulatory program.

Authority for 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) of the PHS Act, any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted (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. The regulations that we have proposed specific to enforcement appear in the GTP proposed rule.

HCT/P's that do not meet FDA's criteria set forth in part 1271 for regulation solely under section 361 of the PHS Act are regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act, and their manufacturers are required to register with the agency under section 510 of the act (21 U.S.C. 360). Regulations implementing section 510 of the act are found in parts 207 and 807 (21 CFR parts 207 and 807), among other parts. In order to consolidate our data base on the cell and tissue industry and thus to improve our oversight functions, we are amending parts 207 and 807 to require registering establishments to follow the procedures set out in part 1271; these amendments are effective in 2 years, when we project the remaining two proposed tissue rules will be ready for implementation. 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 HCT/P's is intended to further the goal of preventing the spread of communicable disease, we are relying on the additional authority of section 361 of the PHS Act for the proposed amendments to parts 207 and 807.

II. Highlights of the Final Rule

A. Plain Language

On June 1, 1998, President Clinton directed Federal agencies to begin using ''plain language'' in regulations and other documents. The goal of the plain language initiative is to publish government documents that are easier to understand.

In response to this initiative, we have written the registration regulation in plain language. We have

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

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

B. Framework of the Final Regulation and Part 1271

When final, new part 1271 will be made up of six subparts. This final regulation contains subpart A (general provisions pertaining to the scope and applicability of part 1271; definitions); and subpart B (registration and listing procedures). The donor-suitability proposed rule contains subpart C of part 1271; and the GTP proposed rule contains subparts D, E, and F.

Section 1271.10, in subpart A, sets out the criteria that form the foundation of our tiered, risk-based approach to regulating HCT/P's. HCT/P's that meet these criteria are subject only to regulation under section 361 of the PHS Act. When all the proposed rules that will make up part 1271 become effective, these HCT/P's would be subject to the regulations in part 1271, and no premarket submissions would be required. (We sometimes refer to these HCT/P's as ''361 HCT/P's.'' This term replaces ''section 361 products,'' which was used in the registration proposed rule.) HCT/P's that do not meet the criteria for regulation as 361 HCT/P's will be regulated as drugs, devices, and/or biological products.

In September 1999, in the donor-suitability proposed rule, we modified proposed §§ 1271.1, 1271.3(e), 1271.10, and 1271.20 as they appeared in the registration proposed rule, and we added new § 1271.15. We made some of these changes to clarify our meaning.

We made other changes so that the provisions on scope and applicability contained in subpart A would apply not only to the registration procedures in subpart B but more generally to the rest of the requirements in part 1271. These changes obviated the need for the addition, in later rulemaking, of new sections dealing with scope and applicability and were consistent with our original regulatory intent, as set out in the proposed approach.

We received comments on the registration proposed rule, and we received additional comments on subparts A and B of part 1271 in response to the donor-suitability proposed rule. To the extent possible we address these comments in this final rule; however, we recognize that additional discussion may be necessary as issues arise in the remaining rules that will makeup part 1271.

C. Staggered Effective Dates

In order to accomplish the goal of staggering the effective dates of the registration and listing regulation for different types of HCT/P's, we have divided the definition of ''HCT/P'' in § 1271.3(d) into two paragraphs. Paragraph (d)(1) of § 1271.3 identifies the subgroup of human tissues defined in part 1270. Paragraph (d)(2) provides the broader definition of HCT/P based on proposed § 1271.3(e). The definition of the subgroup in paragraph (d)(1) incorporates the definition of ''human tissue'' set out in § 1270.3(j) and thus identifies those tissues that are currently regulated under part 1270, including, for example, such tissues as corneas, bone, and skin. This represents the subgroup of human cells, tissues, and cellular and tissue-based products for which this final rule will first go into effect. Paragraph (d)(2) of § 1271.3 provides the broader definition of HCT/P and includes those HCT/P's described in paragraph (d)(1) as well as such additional HCT/P's as reproductive cells and tissues, hematopoietic stem cells, and cells and tissues currently regulated as drugs, devices, and/or biological products. The definition in paragraph (d)(2) of § 1271.3 will eventually replace paragraph (d)(1), as described below.

The effective date of § 1271.3(d)(1) is 75 days after the publication of this rule. The entire definition of HCT/P in § 1271.3(d)(2) is effective 2 years after the publication of this final rule in the **Federal Register**. The effect of this action is to make this final regulation applicable first to those HCT/P's currently regulated under part 1270, and later to the complete range of HCT/P's defined in § 1271.3(d)(2). When all of the regulations that make up part 1271 are final and have superseded part 1270, we will revoke § 1271(d)(1) and renumber (d)(2) as a conforming amendment. At that time the new regulatory framework contained in part 1271 will be instituted as a whole.

D. Other Highlights of This Final Rule

This final rule contains other changes from the proposed rule. Among these changes are the following:

- We have broadened ''family-related allogeneic use,'' as used in proposed § 1271.10, to include first-degree and second-degree blood relatives.
- We have modified the definition of ''homologous use.''
- We have replaced the phrase ''combined with or modified by the addition of a drug or a device'' in § 1271.10 with new language.
- We have deleted the phrase ''pending scheduled'' from the exception in § 1271.15(d) for establishments that only receive or store HCT/P's.
- We have added an exception for establishments that only recovers reproductive cells or tissues for immediate transfer into a sexually intimate partner of the cell or tissue donor. (§ 1271.15(e)).

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

We received 28 comments on the proposed rule as it was published in 1998. We received over 400 comments on the donor-suitability proposed rule; many of these raised issues related to subparts A and B of part 1271.

A. General Comments

(Comment 1) Many comments expressed general approval of the rule. One comment stated that the proposed rule addresses the public health needs for regulation in this area, helping to assure an adequate supply of safe and functional products without imposing unnecessary regulatory burdens or inhibitions to progress. Another comment, in support of registration, noted the importance of establishing a known data base of the industry. Another comment stated that creation of an official inventory of establishments subject to FDA regulation is important to determine the actual level of compliance and to develop reliable estimates of the cost of enforcement.

We acknowledge and appreciate these supportive comments. The new regulation on registration and listing will increase our knowledge and understanding of the HCT/P industry and will enable us to monitor industry developments and communicate with industry members. This final rule will enhance our compliance efforts in protecting the public from the spread of communicable diseases, when the remaining tissue regulations become effective.

(Comment 2) Some comments objected to the development of a comprehensive regulatory system. One of these comments objected that the approach is based on potential, not actual, concerns, is more applicable to new products than to such tissues as corneal tissue offered for transplant, and is unnecessary in light of quality assurance programs established by professional organizations.

We believe that this new regulatory program for HCT/P's, when it is in place, will be superior to the confusing patchwork of requirements that it will replace. We have created a simple registration system with uniform requirements for all HCT/P's and a one-page registration and listing form. The procedures in subpart B of part 1271 will be followed by all HCT/P establishments, along with those in proposed subparts C and D of part 1271. Together, they are intended to establish a communicable disease prevention program necessary to protect the public health.

In developing and issuing the registration rule, we have recognized that, because all HCT/P's are derived from the human body, they share certain common characteristics, among other things the ability to transmit infectious diseases. Thus, basic requirements such as registration, communicable disease screening and testing, and GTP's may reasonably be applied to all HCT/P's. However, we have also recognized that within the larger group of HCT/P's, certain products may present a greater degree of risk, and that these HCT/P's should be subject to additional premarket requirements.

With this tiered, risk-based approach, we will be putting in place a set of baseline requirements for all HCT/P's, while recognizing that different HCT/P's may present different concerns. As the comment points out, some concerns may be more applicable to new products than to such tissues as corneal tissue offered for transplant. We have identified criteria corresponding to the types of reduced risks that certain products may present. HCT/P's that do not meet all of these criteria will be regulated under the act and/or section 351 of the PHS Act (subject to subsequent effective dates). On the other hand, most HCT/P's, including cadaveric corneas, will be regulated solely under the communicable disease authority of section 361 of the PHS Act

and the regulations that will make up part 1271.

When implemented, the registration, donor-suitability, and GTP regulations are intended to reduce the risk of transmission of communicable disease by HCT/P's. The donor-suitability proposed rule incorporates and expands upon many of the requirements for human tissue intended for transplantation in part 1270. The part 1270 requirements were put into place to prevent the transmission of human immunodeficiency virus and hepatitis through the transplantation of tissue from domestic and foreign sources, ''Human Tissue Intended for Transplantation,'' final rule (62 FR 40429, July 29, 1997).

Registration and listing are crucial components of a regulatory program to increase the safety of HCT/P's. Indeed, the United States General Accounting Office (GAO) has urged the agency to put a program in place in response to the potential transmission of infectious diseases from cell and tissue donors to recipients, GAO, ''Human Tissue Banks, FDA Taking Steps to Improve Safety, but Some Concerns Remain'' (December 1997).

We recognize the importance of voluntary quality assurance programs, and we respect the efforts and accomplishments of professional organizations. We have considered the efforts of professional organizations, and we will continue to do so as we implement the new regulations. However, not all HCT/P establishments belong to or are accredited by such groups, and voluntary programs are not enforceable.

(Comment 3) Another comment stated that we should finalize the registration rule as soon as possible, without waiting for the other rules.

We agree that there are benefits to publishing the registration final rule in advance of the other final rules, and we are doing so. However, as discussed earlier in this document, we are staggering the regulation's effective dates. Under this approach, we will be able to promptly begin receiving registration and listing information for HCT/P's currently subject to part 1270.

(Comment 4) One comment asserted that we should identify those tissues and entities subject to part 1271 that are not currently subject to part 1270, and initiate rulemaking to broaden the coverage of the substantive regulations codified in part 1270.

Rather than broaden the scope of the regulations in part 1270, we have earlier noted that we intend to replace part 1270 with the new regulations in part 1271 (donor-suitability proposed rule, 64 FR 52697). Revocation of part 1270 will occur at the time the GTP final rule becomes effective. We have earlier made clear (64 FR 52697 to 52698) that the new rules in part 1271, when complete, will be broader in scope than those in part 1270, will impose additional testing and screening requirements, and will cover more establishments and HCT/P's (e.g., hematopoietic stem cells, reproductive tissue). Thus, it is not necessary to initiate rulemaking to broaden the coverage of the regulations in part 1270.

(Comment 5) One comment asked the agency to clarify if it intends to require registered organizations to pass along any information the agency disseminates. Another comment counseled against depending on a secondary dissemination system, from those required to register to those with whom they interact who are not required to register, to get educational information to all of the tissue community.

We are not imposing a specific information-dissemination requirement at this time. The only members of the tissue community who would be subject to the rules in part 1271 and who are not required to register are those individuals who recover cells or tissue under contract, agreement, or other arrangement with a registered establishment, but who perform no other manufacturing step (except for sending the cells or tissue to the registered establishment). These individuals would be subject to the other requirements that will be contained in part 1271, when complete, and the establishments for whom they perform their services would be responsible for their work. (This exception is discussed in greater detail below.) Therefore, we believe that if we distribute information to registered establishments, we will be reaching the whole of the affected tissue community.

(Comment 6) One comment expressed concern that the proposed rule failed to identify the party ultimately responsible for the tissue or for the decisions required in the process of determining donor and tissue suitability.

We have addressed the question of responsibility in the GTP proposed rule.

(Comment 7) Several comments raised the issue of dispute resolution, particularly with respect to questions about homologous use and minimal manipulation. One of these comments urged us to develop and follow a process for resolving disputes in a prompt and efficient manner. One comment recommended that the Tissue Reference Group (TRG) serve as the forum for resolving any disagreements that arise with regard to the application of definitions.

We recognize that, as we implement this new regulation, there will be areas in which additional guidance may be desirable or interpretations may differ. To help answer questions about how a particular HCT/P will be regulated, the agency developed the TRG. If an establishment is not sure how its HCT/P may be regulated, it should contact the TRG.

The TRG provides a single reference point and makes recommendations to the Center Directors regarding regulation of specific HCT/P's, e.g., regulation solely under section 361 of the PHS Act or additionally under the act and/or section 351 of PHS Act. The TRG is composed of: (1) Three representatives from the Center for Biologics Evaluation and Research (CBER), including the product jurisdictional officer; (2) three representatives from the Center for Devices and Radiological Health (CDRH), including the product jurisdictional officer; and (3) a liaison from the agency's Office of the Chief Mediator and Ombudsman (OCMO), a nonvoting member. Other FDA staff attend the TRG meetings as needed to discuss issues related to products in their area of expertise. Further information about the TRG can be found on CBER's website at http://www.fda.gov/cber/tissue/trg.htm.

In some cases, a product regulated under the act will fall under the jurisdiction of more than one agency component, e.g., a combination device and biological product. Where the agency component with primary jurisdiction is unclear or in dispute, a sponsor may request designation from the product jurisdiction officer, who is the FDA Ombudsman, as detailed in 21 CFR part 3. In addition, the OCMO can assist in resolving disputes with the agency that may arise from decisions made by the Center Directors regarding the regulation of HCT/P's, after consideration of TRG recommendations, as described above.

In addition, we recognize that further public discussion of how tissue regulation would be applied to certain categories of human cells, tissues, and cellular and tissue-based products may be warranted due to the complexity or sensitivity of the issues. For example, we held a public meeting on August 2, 2000, to discuss how proposed definitions for ''minimally manipulated'' and ''homologous use'' should be applied to human bone allograft products (65 FR 44485, July 18, 2000). We intend to provide further opportunities for public discussion of

how the regulatory approach should be applied to other HCT/P's. We anticipate that there may be additional needs for discussion through public meetings, public hearings, or guidance as we implement the new regulations.

(Comment 8) One comment asserted that we have published no document describing the TRG's current composition, authoritative status, procedures, whether its decisions are or will be made public, or how industry is expected to communicate with the group. The comment also suggested that we should consider making the TRG's policy decisions routinely available to the public.

We appreciate these comments and are committed to working on the issues raised. Among other things, the TRG is looking into mechanisms for increasing the transparency of its functions, while still protecting confidential information. Information about the TRG can be found on CBER's website at http://www.fda.gov/cber/tissue/trg.htm.

(Comment 9) Several comments asserted that we are proposing to regulate the practice of medicine, especially with respect to reproductive tissue and hematopoietic stem cells.

We disagree with this comment. This final rule sets out registration and listing requirements for establishments that recover, process, store, label, package, or distribute HCT/P's, or screen or test cell and tissue donors. HCT/P's, including hematopoietic stem cells and reproductive tissues, fall within our jurisdiction. Some HCT/P's will be regulated under the act and/or the PHS Act, while other HCT/P's will be effectively regulated solely by regulations issued under our authority to prevent the spread of communicable disease. We are not attempting to govern practitioners' use of HCT/P's, but rather to ensure that HCT/P's that would be used by practitioners in their treatment of patients are in compliance with applicable regulations, including regulations designed to prevent the transmission or spread of communicable disease.

(Comment 10) We received several comments on our proposed regulation of hematopoietic stem cells. One comment supported the proposal that all establishments involved with hematopoietic stem cell therapy register with FDA. Two comments asserted that the proposed regulation would jeopardize patient treatment, impede the development of new therapies, and increase the costs of treatment. One comment asserted that we lack the legal authority to regulate intrastate hematopoietic stem cell transplants. Another comment argued that clinical research involving the use of blood or bone marrow transplantation for treatment of human diseases, but not involving an investigational drug or device, should not require an investigational new drug application or investigational device exemption. This comment further requested the development of simplified procedures for evaluating those investigational devices or cellular biologic products that are more than minimally manipulated. Two comments argued that there is no need for FDA regulation as industry standards suffice and FDA requirements would be duplicative.

We believe that it is necessary to bring the regulation of hematopoietic stem cells in line with the regulation of other HCT/P's, and that we possess the legal authority to take this action. Like other HCT/P's, hematopoietic stem cells may transmit communicable diseases; thus, the basic communicable disease prevention requirements that will be contained in part 1271, including these registration and listing requirements, are as relevant to these cells as to any other HCT/P's. Intrastate activities involving hematopoietic stem cells, as well as other HCT/P's, can be regulated to prevent the interstate spread of communicable diseases under section 361 of the PHS Act. (See *Louisiana* v. *Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).) The GAO has cited the lack of regulation of hematopoietic stem cells as a significant gap in our oversight, and urged us to proceed with implementing new regulations that would cover hematopoietic stem cells. We are now closing that gap.

Although we applaud the development of industry standards noted by the comments received, such standards are not followed by all HCT/P establishments. Moreover, voluntary standards differ significantly from enforceable regulations. We cannot take enforcement actions to ensure compliance with voluntary industry standards and thus would be limited in our ability to protect the public health if we relied on such standards alone. Establishments that comply with industry standards, however, should have little trouble adapting their practices to the new requirements. Thus, any additional burden should be minimal.

Rather than require data submission from each hematopoietic stem cell establishment, we have considered the development of standards for certain stem cell products. On January 20, 1998 (63 FR 2985), we published a notice in the **Federal Register** requesting the submission of proposed standards and supporting data relating to certain stem cell products by January 20, 2000, entitled ''Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products.'' Later, we extended the deadline for submitting data to July 17, 2000 (65 FR 20825, April 18, 2000).

(Comment 11) One comment generally agreed with our proposal to require registration for certain reproductive tissue, but requested several clarifications and exceptions. Several comments questioned the need for the regulation of reproductive cells and tissues, citing current oversight from professional organizations, other Federal agencies, and States. Comments opposed registration for programs involved in egg donation, egg retrieval, semen processing, semen evaluation, or in vitro fertilization (IVF) in assisted reproductive technologies. One comment asserted that a large number of medical practitioners who perform inseminations would not be included in this new regulation, lessening their effectiveness. Another comment asserted that programs that manufacture tissue culture products for the growth of oocytes and sperm for sale should be required to register, but IVF programs making culture medium for their own uses should be exempt.

We stand by our decision to extend regulatory requirements to reproductive cells and tissue. Currently, FDA does not have regulations in place to address the infectious disease risk of donating, processing, and storing reproductive cells and tissue. Because there has been no registration or listing requirement, we have not had accurate information about the industry. We agree with the GAO that extending regulation to reproductive cells and tissues will remedy a significant gap in oversight.

Although we recognize the value of professional efforts to self-regulate, and of regulatory efforts of other agencies and the States, we disagree that these piecemeal, often voluntary, efforts are adequate. Nor will the new regulations in part 1271 be duplicative. State regulation varies from State to State and does not consistently address our concerns about the transmission of communicable disease. The model certification program for embryo laboratories developed by the Centers for Disease Control and Prevention (CDC) is a voluntary program that States may or may not choose to adopt; its primary focus is not on preventing the transmission of communicable disease. No State has yet adopted CDC's model certification program. Membership in professional societies is voluntary.

Moreover, many establishments do not report to the Society for Assisted Reproductive Technology. The Clinical Laboratories Improvement Amendment of 1988 (CLIA) covers clinical laboratory testing, including certain procedures performed in embryo laboratories; however, as discussed later in this document, CLIA certification is not equivalent to the requirements we are putting in place.

We disagree that establishments that only deal with egg donation, retrieval, semen processing, or IVF should be exempt from the new regulations. These activities are vital to the handling of reproductive tissues. Performing these activities appropriately in order to prevent cross-contamination and mix-ups requires proper recordkeeping, storage practices, and accountability. Moreover, registration of these establishments is consistent with agency practice in other areas; e.g., establishments where only blood donation or processing occurs are required to register.

As discussed later in this document, however, this final rule contains a new exception for certain reproductive tissue establishments that perform only certain limited activities that raise limited communicable disease concerns. Under the exception, an establishment that only recovers reproductive cells or tissue for immediate transfer into a sexually intimate partner of the cell or tissue donor is not required to comply with the requirements that will be contained in part 1271, including registration and listing.

With respect to the comment about tissue culture media, these products are not considered HCT/P's. Rather, embryo culture media and other such products are regulated as medical devices by FDA, and establishments that manufacture embryo culture media are subject to the device regulations.

(Comment 12) Several comments responded to our discussion of regulating dura mater and human heart valve allografts as 361 HCT/P's rather than as devices, if they meet the criteria in § 1271.10 (63 FR 26744 at 26747). Three comments supported the regulation of heart valves as 361 HCT/P's. One comment suggested that, to prevent a regulatory ''open window,'' the regulatory change should not take place until GTP requirements are effective or other steps are taken. One comment asked whether the transfer of heart valves would be reflected in a codified regulation. A fourth comment supported regulating dura mater as a 361 HCT/P and strongly suggested that ''special controls'' be included in the GTP requirements. No comments objected to regulating heart valve allografts and dura mater as 361 HCT/P's.

We agree that we should avoid an ''open window'' where possible. Therefore, we have staggered effective dates for this rule to prevent such an outcome. We do not intend to begin regulating human heart valve allografts and dura mater that meet the criteria in § 1271.10 as 361 HCT/P's until the donor-suitability and GTP components of part 1271 become effective, or other appropriate steps have been taken. The GTP proposed rule contains special requirements for dura mater intended to address the communicable disease concerns about that product. Because § 1271.10 contains the criteria for regulation of HCT/P's as 361 HCT/P's, and we are now reiterating our view that heart valves meeting those criteria will not be regulated as devices, we do not intend to issue a separate regulation to change regulatory authority on that specific point.

(Comment 13) One comment suggested that we consider voluntary accreditation and inspection programs in implementing our regulatory strategy. The comment further requested that we accord ''deemed status'' to certain accredited facilities.

We are exploring various options for inspections and compliance actions to enforce the new regulations. Among other ideas, we are looking into those suggested by this comment, including the legal issues raised. At present, we have in place a tiered inspection approach to enforce the regulations in part 1270 that takes into consideration such factors as professional accreditation. We intend to provide a more detailed discussion of our regulatory intentions after consideration of comments to the GTP proposed rule.

(Comment 14) One comment noted that tissue recovery is frequently performed by organ procurement organizations, and that the requirements with regard to the prevention of infectious disease transmission are appropriately much less stringent for organ donation than are comparable requirements for tissues. The comment asserted that exempting these organizations from regulation would immeasurably weaken the public health protection provided by this regulation.

An organ procurement organization that also recovers cells or tissues in addition to organs is not exempt from these regulations, and must register with the agency and follow all other regulations applicable to its actions with respect to HCT/P's. An organ procurement establishment is not required to submit a list of the vascularized human organs for transplantation that it recovers, because these organs are not covered by the definition of HCT/P (see § 1271.3(d)(2)(i)). However, such an organization must list with the agency any HCT/P's that fall within the scope of part 1271 that the organization recovers or otherwise manufactures.

B. Comments on Subpart A of Part 1271: Definitions

We received comments on many of the proposed definitions in § 1271.3(a) through (h). We did not receive comments on the definitions of ''autologous'' and ''transfer.'' We address many of these comments below. Comments on the definitions of ''homologous use'' and ''minimal manipulation'' are addressed in section III.C of this document.

(Comment 15) The definition of *establishment* in proposed § 1271.3(b) reads as follows:

> *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* (emphasis added).

Comments raised issues about the proposed exception in the last sentence of the definition. Some comments asserted that individuals or organizations engaged solely in procurement under contract should be required to register. One comment pointed to the critical role in the suitability assessment of a cell and tissue donor that such organizations play. Another comment asserted that registration and listing should be applied to those who screen donors and that procurement of tissue that is not done in an aseptic manner places tissue recipients at risk. One comment expressed confusion about the exception and suggested that ''or under contract'' should read ''and under contract.'' This comment further suggested that individuals and other legal entities engaged solely in procurement or recovery be required to register unless contracted for that activity to a registered establishment.

Three comments argued for an expanded exception. One comment urged us to clarify that the ''under

contract to'' language can apply to other contracting individuals, not just to contractors engaged in procurement or recovery (e.g., sales representatives who distribute HCT/P's). Two other comments requested clarification that clinical laboratories who perform testing are excluded from the registration and listing requirements.

We have rewritten the exception and moved it to § 1271.15(f). The relevant language now states:

> (f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.

We believe this new language addresses many of the comments' concerns. We have replaced ''or under contract'' with ''and under contract, agreement, or other arrangement.'' In addition, because ''procurement'' and ''recovery'' refer to the same action—the removal of cells or tissue from a donor—we have decided that it is redundant and possibly confusing to use both words. Instead, the exception now uses the term ''recovery,'' the same term used in the definition of ''manufacture'' in § 1271.3(e). Therefore, the exception only applies to those individuals engaged solely in recovery of HCT/P's and who are under contract, agreement, or other arrangement with a registered establishment. We believe this is an appropriate way of easing the regulatory burden on individuals while ensuring the protection of the public health.

This exception does not extend to an individual who does more than recover tissue and send it to the contracting establishment. (Thus, for example, an individual engaged in any aspect of donor screening is not covered by the exception and must register.) Further, an individual who meets the terms of the exception would be excepted only from registration and listing requirements and would be required to comply with all other requirements to be contained in part 1271.

We are not extending the exception to ''other legal entities.'' Only individuals are covered. Examples of such individuals not required to register might include certain medical examiners, morticians, or physicians who recover hematopoietic stem cells or tissues (e.g., corneas, cord blood). Laboratories that perform donor testing are not excluded from registration, listing, or other requirements in part 1271.

(Comment 16) We proposed to define *family-related allogeneic use* in proposed § 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.'' Under § 1271.10(d), as proposed, HCT/P's with a systemic effect that are for family-related allogeneic use would be regulated under section 361 of the PHS Act (provided that the HCT/P meets all other criteria set out in § 1271.10). This limited exception from the requirement for investigational use exemptions and premarketing submissions was first proposed in the proposed approach (62 FR 9721). In the registration proposed rule, we specifically requested further comments on the issue (63 FR 26744 at 26750).

We received approximately 13 comments on our proposed definition of ''family-related allogeneic use,'' most from individuals and organizations involved in hematopoietic stem cell transplantation. One comment praised the proposed definition as clearer and more consistent than that used in the proposed approach, but cautioned that our terminology might create confusion. Other comments argued that we should expand the definition to more distantly related family members. Several comments suggested that the term include all ancestral relations, siblings, and collateral relations to the fourth degree by blood, marriage, or adoption. Another comment objected to distinguishing between family-related donors and other donors, stating that the same principles apply in both situations. This comment argued that the clinical use of unrelated versus related allogeneic transplants falls within the practice of medicine and should not be regulated by FDA.

We have decided to change the term from ''family-related allogeneic use'' to ''allogeneic use in a first-degree or second-degree blood relative.'' Parents, children, and siblings are considered first-degree relatives. Aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren are second-degree relatives. Relations by adoption or marriage are not included. Because we are using the phrase ''first-degree or second-degree blood relative'' in its ordinary sense, the final regulation does not contain a definition of this phrase.

Our decision to broaden the scope of related donors to include second-degree blood relatives, rather than just first-degree, is based upon several factors. In the absence of a human leukocyte antigen (HLA) identical sibling, the search for donors in extended families is occurring now to a very limited degree, but is likely to increase with the continuing advances in deoxyribonucleic acid technology. The likelihood of finding a donor with a haplotype identical to that of the recipient is greater among blood-related individuals than among unrelated individuals. Indeed, statistical methods have been proposed to measure this probability (Refs. 2 and 3).

In addition, for certain ethnic groups, it is extremely difficult to find an appropriate unrelated donor. Success at finding a match among the extended family can be equal to or even greater than the chance of finding a match using a single sibling search, if the haplotype is a common one within the patient's ethnic population, and the family members are of the same ethnic origin.

Registry outcome data for some hematologic malignancies suggest that peripheral blood and bone marrow transplant recipients may have a better survival rate when transplanted with hematopoietic stem cells from related donors. One possible reason is that a related donor is likely to share identical haplotypes with the patient (the genotypic level), whereas an unrelated donor is matched at the phenotypic level. Also, family donors may be better matched for minor histocompatability loci for which testing is not routinely performed.

We initially proposed a more limited exception. Having reviewed the comments on this issue, we believe there is some scientific merit in expanding the exception to second-degree blood relatives. This change is consistent with our goal of keeping regulatory burden to a minimum. The same scientific justification does not exist for expanding the exception to relatives by marriage or adoption, and is weaker for blood relatives beyond the second degree. In addition, the exception in § 1271.10(a)(4)(ii)(*b*) for allogeneic use in a first-degree or second-degree blood relative does not extend to those situations where the HCT/P is more than minimally manipulated, is advertised, labeled or otherwise objectively intended by the manufacturer for a nonhomologous use, or is combined with a drug or device (except as described in § 1271.10(a)(3)).

(Comment 17) One of the comments on ''family-related allogeneic use'' asserted that, in the context of reproductive medicine, the notion of appropriate use of family-related materials must include the close blood relatives of either partner. This

comment proposed that those facilities collecting or using reproductive tissues from sexually intimate partners or close relatives should not be required to register.

Later in this document, we address the question of registration for reproductive tissue facilities. The change in terminology from ''family-related allogeneic use'' to ''allogeneic use in first-degree or second-degree blood relatives'' does not affect the registration of reproductive tissue establishments.

(Comment 18) Several comments objected to the word ''product'' in the term *human cellular or tissue-based product*, defined in proposed § 1271.3(e). These comments asserted that human cells and tissues are donations, not goods manufactured for sale. Some comments argued that the use of the word ''product'' might have legal implications; e.g., subjecting eye banks to inappropriate product liability litigation. Comments also noted that the word ''product'' is inconsistent with terms used in the tissue and eye banking field. We also received an objection to describing embryos and germ cells as ''products.''

In choosing ''human cellular or tissue-based product,'' we were seeking a term that would describe everything that will be subject to the regulations in part 1271. We needed a term broad enough to cover both cells and tissues, and one that would include within its scope such diverse articles as unprocessed tissue, highly processed cells, and tissues that are combined with certain drugs or devices. Although we have considered removing the word ''product'' from the definition, we are concerned that another term (e.g., ''human cells and tissues'') would not be understood to include many of the highly manufactured products to which the regulations apply, or might be misconstrued to apply only to the cell or tissue component of such a product. Moreover, the term ''product'' is consistent with the language of the statutes under which we operate; for example, blood (which is also routinely donated) is a ''biological product'' under section 351 of the PHS Act. We do not believe that the use of the word ''product'' will affect the manner in which state laws apply to HCT/P's; our experience with the regulation of blood and blood products supports this view.

We recognize, however, that conceptual difficulties may arise in calling certain cells or tissues ''products.'' Thus, as noted earlier in this document, we have expanded the term to ''human cells, tissues, and cellular and tissue-based products,'' abbreviated as ''HCT/P's.'' We have made appropriate substitutions throughout the regulation. The definition itself has not changed, and the scope of the term remains the same.

Proposed § 1271.3(e) has been redesignated as § 1271.3(d)(2).

(Comment 19) One comment stated that the proposed rule leaves vague peripheral blood lymphocytes that are not cultured or manipulated, but are used for their immunological effects for the treatment of disease. According to the comment, the definition in proposed § 1271.3(e)(2) (final§ 1271.3(d)(2)(ii)) implies that these cells are subject to regulation under 21 CFR part 607. The comment recommends that these cells be specifically included in this proposal and not be considered mature blood cells subject to regulation under other sections of title 21 of the CFR.

We believe that the commenter is addressing donor lymphocytes (leukocytes) for infusion (DLI), which are the lymphocyte-rich cellular fractions obtained by leukapheresis of the peripheral blood of donors of bone marrow or peripheral blood hematopoietic stem/progenitor cells. Many DLI products are not further manipulated. These minimally manipulated products are administered to select patients to elicit a graft-versus-leukemia effect and to treat other transplant-associated complications.

DLI, regardless of the level of manipulation, meet the definition of HCT/P in this rule. FDA intends to regulate all DLI as HCT/P's, rather than as traditional blood products.

(Comment 20) One comment on proposed § 1271.3(e) requested clarification that an extract would not fall under the definition of human cellular or tissue-based product. The comment noted that the words ''any cell or tissue-based component of such a product'' may imply that an extract could fall within the definition.

We do not consider extracts to be HCT/P's. When we revised the definition of human cellular or tissue-based product in the donor-suitability proposed rule (64 FR 52696 at 52719), we deleted the phrase ''or any cell or tissue-based component of such a product.'' Moreover, we listed ''any secreted or extracted human products'' as an exception to the definition of HCT/P in proposed § 1271.3(e)(3). These changes are codified in this rule at § 1271.3(d)(2)(iii).

(Comment 21) One comment on proposed § 1271.3(e)(4) objected to the exclusion of bone marrow from the definition of HCT/P, since all three sources of hematopoietic stem cells (cord, peripheral blood, bone marrow) have the same risk of infectious disease transmission.

Minimally manipulated bone marrow falls under the purview of the Health Resources and Services Administration (section 379 of the PHS Act (42 U.S.C. 274(k)). For this reason, we have excepted it from the definition of HCT/P's, and thus from the scope of this regulation issued under section 361 of the PHS Act authority.

The exception for bone marrow in final § 1271.3(d)(2)(iv) extends only to ''minimally manipulated bone marrow for homologous use and not combined with a drug or a device (except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow).'' Bone marrow would meet the definition of an HCT/P if it is: More than minimally manipulated; advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use, or combined with certain drugs or devices.

(Comment 22) In the proposed rule, we stated in proposed § 1271.3(f) that ''*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'' (63 FR 26744 at 26754). Approximately 10 comments objected that the term ''manufacture'' is inappropriate. Some comments asserted that fertility clinics are not ''manufacturers'' of human tissue. Comments from the eye banks asserted that it is inaccurate to use the word ''manufacture'' with respect to corneal tissue; along with ''product,'' the term could raise legal issues (e.g., subjecting eye banks to inappropriate product liability litigation). Another comment asserted that tissue banks do not manufacture tissue, but rather process it.

We have considered substituting a different term for ''manufacture,'' but have been unable to find a satisfactory replacement. Most of the terms that we considered (e.g., produce, handle) were too limited in scope. Moreover, comments that objected to the term did not suggest alternatives. For these reasons, we continue to use the word ''manufacture'' as an umbrella term to capture the many different actions that HCT/P establishments might take in preparing HCT/P's for use. These steps may include, but are not limited to, recovery, screening, testing, processing, storage, labeling, packaging, and distribution. No comments disagreed with or objected to any of the actions listed in the definition of manufacture.

Rather than list each of these activities repeatedly throughout this preamble and the regulation, we have decided to maintain the term ''manufacture,'' as defined in this rule (proposed § 1271.3(f) is codified at § 1271.3(e)).

(Comment 23) One comment on *manufacture* questioned the rationale for requiring testing establishments to register. Three comments asserted that testing laboratories should not be required to register because CLIA certification is sufficient. One comment asked if labs that test for other diseases or that perform bacterial cultures need to register.

The definition of ''manufacture'' is intended to cover all steps in the process of handling HCT/P's. Testing donors for communicable diseases is a critical step in this process and for that reason is included the definition of manufacture. The registration requirement for testing laboratories enables us to have a list of all parties involved in manufacturing activities.

Having a list of testing laboratories enables us to inspect laboratories to ensure that testing is performed in a correct manner according to test kit instructions. The CLIA certification referred to in the comments is important, and in fact we are requiring CLIA certification. However, because there are differences between inspections under CLIA and inspections carried out by FDA, CLIA certification alone is not adequate for our purposes. CLIA requirements address only a limited spectrum of laboratory testing and personnel requirements and do not focus on donor testing. Moreover, our experience with inspecting testing laboratories indicates that significant violations have been found. To exclude testing laboratories from the scope of this regulation would not be consistent with our goal of preventing the transmission of communicable diseases.

The registration requirement for testing laboratories extends to those laboratories that test donor specimens for communicable disease. Only laboratories that test for relevant communicable diseases as defined in the proposed donor-suitability rule are required to register. We have clarified the definition of ''manufacture'' to refer to ''screening or testing of the cell or tissue donor'' rather than to screening or testing of the cell or tissue. In the situation where communicable disease testing to determine donor suitability might be appropriately performed on the cells or tissues, rather than on the donor (as might be the situation with cord blood), such testing would be included within the meaning of donor testing.

(Comment 24) One comment noted that entities engaged only in labeling and packaging are not explicitly within the scope of part 1270, but are covered by this new rule.

Part 1271 covers more activities than part 1270.

(Comment 25) In the preamble to the proposed rule, we noted that *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'' (63 FR 26750). We have proposed a codified definition of ''distribution'' in the GTP proposed rule.

For purposes of the regulations in part 1271 only, we have proposed in the GTP rule to define ''distribute'' to mean the conveyance or shipment of an HCT/P. In other contexts, FDA has defined ''distribution'' more broadly. Under the act, FDA has interpreted the term ''distribute'' to include the delivery, transfer, and dispensing of products. Moreover, the ordinary, dictionary meaning of the term ''distribute'' includes acts such as delivering, dispensing, supplying, and giving out. In this rule, we do not intend the term to include the dispensing or the transfer of an HCT/P to or in a patient.

Two comments on the registration proposed rule disagreed with the phrase ''whether or not possession is taken.'' They asserted that merely taking orders for a product should not be included within the meaning of ''distribution,'' and thus should be excluded from ''manufacture.'' One of these comments described its ''service and distribution'' agreement with a tissue processor, noting that although it does not ship or take possession of the product, its name appears on the product label along with that of the processor. A third comment recommended that the term ''distributes'' be clarified to exclude ''distributors''; i.e., organizations that receive processed/manufactured allografts and ship them to hospitals. Another comment noted that hospitals and other establishments sometimes provide tissue to other institutions in emergencies or in cases of special need. The comment requested that these limited activities not be considered distribution.

We agree that an entity that does not take possession of HCT/P's is not distributing them for the purposes of this rule. However, we disagree that distributors should be excluded from the terms of the definition of ''distribution.'' We agree that the occasional provision of HCT/P's to other institutions on an emergency basis does not fall within the meaning of ''distribution.''

We will consider any additional comments on the definition of ''distribution'' when finalizing the other proposed rules that will make up part 1271.

C. Comments on Subpart A: Proposed §§ 1271.10 and 1271.15 (Final §§ 1271.10 and 1271.20)

In proposed § 1271.10, we set out the criteria for regulating certain HCT/P's solely under section 361 of the PHS Act and the regulations to be contained in part 1271. An HCT/P would be subject to this level of regulation if it: (1) Was minimally manipulated; (2) was not promoted or labeled for any use other than a homologous use; (3) was not combined with or modified by the addition of any component that is a drug or a device; and (4) either does not have a systemic effect, or has a systemic effect and is for autologous, family-related allogeneic, or reproductive use (64 FR 52720).

Proposed § 1271.15 was intended to describe the HCT/P's that did not meet the criteria set out in § 1271.10 and for which we therefore did not consider regulation solely under section 361 of the PHS Act to be justified (64 FR 52699). The section set out the ''mirror images'' of the criteria in § 1271.10 to assist readers in understanding which HCT/P's would not be regulated solely under part 1271. However, rather than providing clarification, the proposed section could have been interpreted to create an additional hurdle for regulation of certain HCT/P's as drugs, devices, and/or biological products.

Our ability to regulate an HCT/P as a drug, device, and/or biological product derives from the act and section 351 of the PHS Act, authorities that are distinct from our authority to issue regulations to prevent the transmission of communicable disease under section 361 of the PHS Act. If an HCT/P does not meet the criteria in § 1271.10 for regulation solely under section 361 of the PHS Act, and the establishment does not qualify for any of the exceptions in final § 1271.15, the HCT/P will be regulated under the act and/or the PHS Act and applicable regulations. As part of this rulemaking process, we are amending certain drug and device regulations (e.g., §§ 207.20, 807.20) to require compliance with certain subparts of part 1271.

Therefore, we have modified proposed § 1271.15 and renumbered it § 1271.20. That section now refers to ''an HCT/P that does not meet the

criteria set out in § 1271.10(a),'' rather than setting out the mirror images of those criteria. As before, the section contains cross-references to those drug and device regulations (e.g., §§ 207.20 and 807.20) that will direct establishments to follow the procedures set out in subparts B, C, and D of part 1271. The section now also clarifies that the referenced drug and device regulations apply if the establishment does not qualify for any of the exceptions in § 1271.15.

We address below the comments received on proposed § 1271.10 and on the proposed definitions of ''homologous use'' and ''minimal manipulation.''

(Comment 26) One comment requested that we schedule a public meeting to discuss the appropriateness, legality, and practicality of using the criteria in § 1271.10 to reach jurisdictional determinations.

We value public input on the criteria in § 1271.10. In February 1997 we made available the proposed approach, which among other things described the factors that we would consider in choosing to regulate certain HCT/P's solely under the authority of section 361 of the PHS Act rather than as drugs, devices, and/or biological products. On March 17, 1997, we held a public meeting to solicit information and views on the proposed approach from the interested public, and we opened a docket for the submission of comments (Docket No. 97N–0068).

We have published three proposed rules in the **Federal Register**. Two of those rules specifically solicited comments on the criteria for regulating certain HCT/P's solely under section 361 of the PHS Act. On August 2, 2000, we held an open public meeting to solicit information on current practices related to the manipulation and homologous use of human bone allograft in the spine and other orthopedic reconstruction and repair. Many of the comments presented at the meeting indicated that there were misunderstandings about how the criteria set out in § 1271.10 would be applied, and about the meaning of the terms ''minimal manipulation'' and ''homologous use.'' This final rule contains clarifications and additional examples that we believe will clear up much of the confusion expressed at the meeting. We will consider issuing a guidance document if establishments need additional help in understanding the terms.

We intend to schedule additional public meetings as necessary. For example, FDA believes that additional public discussion of how the criteria in § 1271.10 would apply to reproductive tissues would be helpful, and further development of policy in this area may be warranted.

(Comment 27) We received numerous comments on the definition of *minimal manipulation*. The proposed definition reads as follows:

> *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.

One comment urged us to state in the preamble of the final rule those activities that FDA presently considers to be minimal manipulation. Two comments recommended that the following procedures be considered minimal manipulation: Selective removal of B-cells, T-cells, or malignant cells; blood or platelet depletion; centrifugation; density gradient separation; and cryopreservation. Two comments supported the use of clinical and scientific data to determine whether a tissue-processing method is appropriately considered to be minimal manipulation or more than minimal manipulation.

Eight comments asserted that ''minimal manipulation'' is vague and open to subjective interpretation, and should be eliminated. Two comments asserted that it is difficult to draw a meaningful distinction between tissues that are minimally manipulated and those that are more than minimally manipulated. One of these comments suggested that instead of the minimal manipulation criterion, FDA should propose that tissue products labeled or promoted for tissue replacement, reconstruction, or restoration of function be regulated as tissue. Another comment requested the development of guidance and noted that, in light of future technological advances, a broader definition of minimal manipulation may be more appropriate. One comment recommended that the TRG serve as the liaison for communicating with manufacturers concerning FDA's intended application of the definition of minimal manipulation to particular tissues.

We received many comments on the regulation of bone allografts, INCLUDING bone dowels, submitted in response to the donor-suitability proposed rule. (The agency had previously considered regulating certain bone dowels as medical devices.) Many of these comments addressed the concept of minimal manipulation. Several comments supported regulating machined bone allografts as medical devices in order to evaluate their safety and efficacy and protect the public health. However, most comments opposed such regulation, pointing to the long history of safe use of bone allografts and citing concerns about decreased supply, among other issues.

Comments did not suggest changes to the definition of minimal manipulation, and we have not changed the regulation's wording. We disagree that the term should be eliminated, however, as it serves as a valid indicator of those HCT/P's that present fewer risks and that are most appropriately regulated solely under section 361 of the PHS Act and part 1271 (so long as other criteria are also met).

We agree that the TRG will continue to play a role in providing recommendations for certain decisions made by the Center director interpreting the term ''minimal manipulation.'' At this time, examples of HCT/P's that we consider to be minimally manipulated include those that have been subjected to the following procedures: Density gradient separation; selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing. We do not agree that the expansion of mesenchymal cells in culture or the use of growth factors to expand umbilical cord blood stem cells are minimal manipulation.

Most of the comments we received on the regulation of bone allografts and bone dowels assumed that we planned to regulate all bone allografts as medical devices. This is a misunderstanding. We are not considering regulating all bone allografts as medical devices. Like all other HCT/P's, the regulation of bone allografts depends on the four factors set out in § 1271.10. If the allograft is minimally manipulated, is not advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use, and is not combined with a drug or device (except as described in § 1271.10(a)(3)), then it will be regulated as a 361 HCT/P and subject only to the regulations in part 1271. (Bone allografts do not have a systemic effect, so the fourth factor is not at issue.) We consider cutting, shaping and grinding of bone minimal manipulation. Threading and other machining procedures that are performed to create bone dowels, screws, and pins are also considered minimal manipulation.

(Comment 28) We received many comments on the term *homologous use*, which we defined in proposed § 1271.3(d) as follows:

> *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.

One comment praised the definition as reasonable, but urged us to develop a process for resolving differences of opinion between FDA and tissue manufacturers. Another comment supported our preamble statement that the ''[b]asic 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'' (63 FR 26744 at 26749). As an example, this comment pointed to surgical use of fascia lata or pericardium allografts to replace or repair damaged dura mater or to construct a bladder support sling from a fascia lata allograft to prevent incontinence. Another comment questioned whether the homologous/nonhomologous criterion is a meaningful indicator of the need for premarket review; this comment cited fascia lata as an example of a tissue that has been used safely and effectively for years in ways that may be considered nonhomologous. One comment in response to our statement (63 FR 26744 at 26749) that the use of hematopoietic stem cells for treatment of adrenal leukodystrophy is an example of nonhomologous use stated that logical application of hematopoietic stem cells for their known hematologic, immunologic or metabolic effects as treatment of human disease should be considered within the practice of medicine and not subject to regulation by FDA.

Approximately 10 comments argued that the term ''homologous use'' should be eliminated. Many of these comments asserted that the term is vague and open to subjective interpretation. One comment stated that the phrase ''fulfills in its native state'' implies that tissue must be used in the identical place and for identical purposes, which ignores the realistic use of most tissue products. Many comments questioned the application of the term ''homologous use'' to bone allografts. One asserted that it is unusual for allograft tissues to be used in a homologous location, especially with regard to the spine.

Below, in comment 29, we discuss our decision to look not at the actual use of an HCT/P, but at the manufactuer's objective intent for a nonhomologous use. Under this approach, a practitioner could use an HCT/P, such as hematopoietic stem cells or fascia lata, for a nonhomologous use in the treatment of the physician's patients. Thus, we would not look at the surgical use of HCT/P's such as fascia lata or pericardium allografts, but instead at whether they were advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use. In the absence of advertising, labeling, or other indications of the manufacturer's intent for such use, we would not require premarket submissions. Should such review be required for a product that has been used safely and effectively for years in nonhomologous ways, and that is intended for a nonhomologous use, we would expect that data would already exist to facilitate the review process.

We disagree that the term ''homologous use'' should be eliminated as a criterion for regulation of human cells or tissues under section 361 of the PHS Act. Regulation solely under section 361 and part 1271 is not warranted unless it is clearly demonstrated that the use of an HCT/P in the recipient is homologous to the function the HCT/P would carry out in the donor. We continue to consider nonhomologous use to be a meaningful indicator that regulation solely under section 361 of the PHS Act is not sufficient. For example, promotion of an HCT/P for an unproven therapeutic use, such as curing cancer, would clearly make it inappropriate to regulate the HCT/P solely under section 361 of the PHS Act and the regulations that will be in part 1271.

We have, however, rewritten the definition of homologous use in response to the comments' concerns. The new definition (codified at § 1271.3(c)) reads: ''Homologous use means the replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.'' The rewording eliminates the distinction between, on the one hand, structural tissues and, on the other, nonstructural tissues and cells. The new wording does not include the statement that, for structural tissues, homologous use occurs ''in a location where such structural function normally occurs.'' This language was understood, contrary to our intention, to limit the use of structural tissue to the same location from which is was derived. However, a use of a structural tissue may be homologous even when it does not occur in the same location as it occurred in the donor. For example, the use of bone for repair, replacement, or reconstruction anywhere in the skeleton of the recipient (including the vertebral column) would be considered homologous use. However, it should be understood that, for the use of a structural tissue to be considered homologous, the HCT/P must perform the same basic function or functions in the recipient as it did in the donor; the use of structural tissue in a location where it does not perform the same basic function as it did in the donor would not be homologous.

We intend to interpret ''nonhomologous'' narrowly. Examples of uses that would be considered nonhomologous include: The use of dermis as a replacement for dura mater, the use of amniotic membrane in the eye, and the use of cartilage in the bladder. As noted above, an HCT/P that is intended by the manufacturer for one of these uses would not be regulated solely under section 361 of the PHS Act and these regulations, but as a drug, device, and/or biological product.

(Comment 29) We received approximately six comments agreeing with our focus in proposed § 1271.10(b) on the promotion or labeling of HCT/P's for nonhomologous uses, rather than on their actual use. One of these comments noted that the use of a product should be determined not by the practice of surgeons but by the promotion, labeling, and objective intent of the manufacturer. Another noted that the manner in which we intend to determine homologous use is consistent with the way we determine the intended use of other products under our jurisdiction. Two comments interpreted proposed § 1271.10(b) as relieving clinicians from restrictions on use of tissue, and one of these comments asserted that the exception should be extended to certain clinical transplant programs.

Another supportive comment questioned how we will regulate the labeling of 361 HCT/P's. Among other things, the comment asked whether we will require 361 HCT/P's to be labeled for their homologous use. The comment also queried whether cutting, shaping, or processing a product in a manner that makes it amenable to nonhomologous use would be considered promotion, in the absence of labeling or advertising.

We appreciate the comments on this issue, and we have decided to maintain the regulation's focus on the objective intent of the HCT/P's manufacturer for a nonhomologous use, rather than on

the intent of the practitioner who uses the HCT/P. We believe this approach will lead to more efficient use of our resources. The focus on labeling, advertising, and other indications of the manufacturer's objective intent does not relieve clinicians from all restrictions on the use of HCT/P's. However, it does mean that clinical use of an HCT/P in a nonhomologous manner, whether by an individual practitioner or a transplant program, can be consistent with regulation of the HCT/P solely under section 361 of the PHS Act and the regulations to be contained in part 1271. In order to clarify this provison, we are revising proposed § 1271.10(b) to read, in new § 1271.10(a)(2), as follows: ''The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent.

By labeling, we refer to the HCT/P label and any written, printed, or graphic materials that supplement, explain, or are textually related to the product, and which are disseminated by or on behalf of its manufacturer. We will address specific labeling requirements after reviewing comments to the GTP proposed rule.

In order to be more consistent with terminology used by the rest of the agency, we have replaced the word ''promoted'' with ''advertised.'' The terms ''advertised,'' ''advertisement,'' and ''advertising'' include information, other than labeling, that originates from the same source as the product and that is intended to supplement, explain, or be textually related to the product (e.g., print advertising, broadcast advertising, electronic advertising (including the Internet), statements of company representatives).

(Comment 30) As originally proposed, § 1271.10(c) contained the following criterion for regulation of an HCT/P solely under section 361 of the PHS Act: ''Not combined with or modified by the addition of any nontissue or noncellular component that is a drug or a device.'' We modified that wording in the donor-suitability proposed rule by deleting the phrase ''nontissue or noncellular.''

Two comments questioned the meaning of § 1271.10(c) and requested additional explanation. For example, the comments asked whether we would regard a component as being a drug or device based on its actual function in the product, or based on how the component is already regulated. The comments also questioned whether all products containing a ''nontissue or noncellular component that is a drug or device'' would automatically be subject to regulation and premarket review as drugs or devices, and expressed concern that application of the criterion might result in unnecessary regulation of HCT/P's as drugs or devices. Another comment asserted that we should not regulate a product containing a drug or device component unless it could affect recipient safety, and that the manufacturer should make the initial determination of whether this threshold has been crossed. One comment stated that hematopoietic stem cell components are routinely processed using centrifuges and other laboratory equipment, combined with dimethylsulfoxide (DMSO) and other reagents for cryopreservation, and separated using devices approved for the processing of hematopoietic stem cells components, and that we have previously classified these steps as minimal manipulation. The comment expressed concern that these steps might be considered to combine the cells with a drug or device component.

In response to the concerns expressed by these comments, we have rewritten the proposed language. Proposed § 1271.10(c) has been renumbered as § 1271.10(a)(3), and now reads: ''The manufacture of the HCT/P does not involve the combination of the cell or tissue component with a drug or a device, except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P.''

The addition of a drug or a device to the cell or tissue component of an HCT/P may ordinarily be expected to add a therapeutic effect and may also raise safety concerns. For these reasons, the addition of a drug or a device to a cell or tissue makes it no longer appropriate to regulate the HCT/P solely under section 361 of the PHS Act. (As used, the terms *drug* and *device* are defined in section 201(g) of the act (21 U.S.C. 321(g)).

However, we recognize that the use of certain sterilizing, preserving, and storage agents do not raise the same concerns. For this reason, we have excepted sterilizing, preserving, and storage agents, but only if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P. Examples of substances that would generally be acceptable include: (1) Cryoprotectants (e.g., DMSO); (2) chemicals used for sterilization (e.g., ethylene oxide); and (3) storage solutions. We encourage the development of industry standards that describe the safe use of sterilization, preserving, and storage agents.

Some drugs or devices that have as their principal purpose sterilizing, preserving, or storage may also have a therapeutic effect or may be claimed to have such an effect. The addition of such drugs or devices would not fall within the exception for sterilizing, preserving, and storage agents. We agree that the establishment that manufactures the HCT/P should make the initial determination of whether the addition of a drug or device that is a sterilizing, preserving, or storage agent to an HCT/P raises new clinical safety concerns.

(Comment 31) We received one comment in response to our request for comments on whether the term ''systemic effect'' adequately characterizes those HCT/P's that should be regulated under section 351 of the PHS Act, such as neural-derived tissues and cells used to replace or supplement neurons in the brain (donor suitability proposed rule, 64 FR 52699). This comment expressed concern that the intent of the proposed change is vague and that currently there is little or no evidence that supports such cells or tissues having any systemic effect when implanted in the brain.

After further consideration, we agree that the term ''systemic effect'' may not cover all of the HCT/P's that we intended to cover. Because the effect of implanted neurons or neural tissue into the brain would likely be restricted to the site where the tissue/cells were placed, this effect might not be included within the meaning of systemic. However, as discussed in the proposed approach, HCT/P's that rely on living cells for their primary function, such as neuronal tissue, raise clinical safety and effectiveness concerns that are not appropriately addressed solely under section 361 of the PHS Act. Such concerns include viability, efficacy, malignant transformation, or rejection after transplantation. Thus, although neuronal cells may not be considered to have a systemic effect, they nonetheless require regulation under the act and/or section 351 of the PHS Act.

Therefore, we have clarified § 1271.10(a)(4) to indicate that an HCT/P that either has systemic effect or depends upon the metabolic activity of living cells for its primary function would not be appropriately regulated solely under section 361 of the PHS Act, and therefore will be regulated as a drug, device, and/or biological product. Cells or tissues such as pancreatic islet cells, which have effects on many different organs throughout the body through the secretion of insulin, are appropriately characterized by the term ''systemic effect.'' Neurons for implantation in the brain would fall into the category of HCT/P's that depend upon the metabolic activity of living

cells for their primary function. In contrast, some HCT/P's (such as corneas, skin, or osteochondral allografts) may contain living cells, but do not depend on them for their primary function, which is structural.

(Comment 32) Two comments on proposed § 1271.10 suggested that isolated human hepatocytes intended for transplantation be considered to meet the criteria in § 1271.10 and therefore be regulated as 361 HCT/P's.

We do not consider human hepatocytes, isolated in tissue culture medium, infused into the spleen, and intended for temporary treatment of liver failure to be suitable for regulation solely under section 361 of the PHS Act. Human hepatocytes have a systemic effect. Therefore, regardless of the level of manipulation of the hepatocytes, these cells would be regulated under the act and section 351 of the PHS Act.

D. Comments on Subpart A: Proposed § 1271.20 (Final § 1271.15)

Proposed § 1271.20, as modified in the donor-suitability proposed rule, set out four specific exceptions from the requirements of part 1271. We address comments on these proposed exceptions below. In this final rule, we have renumbered proposed § 1271.20 as § 1271.15.

(Comment 33) We received one comment on the proposed exception in § 1271.20(b) for establishments that remove human cells or tissues from an individual and implant such cells or tissues into the same individual during the same surgical procedure. The comment assumed that hospitals retaining autologous tissue, not used in a scheduled surgical procedure, to be used in a subsequent application on the same patient, are exempt from registration and listing because the two applications are essentially a single continuous procedure.

We agree that, so long as the hospital does not engage in any other activity encompassed with in the definition of ''manufacture,'' the hospital would not be required to register or comply with the other provisions to be codified in part 1271. For example, if the hospital expanded the cells or tissues, it would not meet the terms of the exception. In reaching this conclusion, we note that hospitals that store autologous cells or tissues for subsequent application in the same patient must follow the guidelines of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) for tissue storage, monitoring of storage devices, and tracking in order to obtain or maintain accreditation.

(Comment 34) We received comments questioning the proposed exception in § 1271.20(d) for establishments that ''receive or store human cellular or tissue-based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility.'' Approximately eight comments asserted that hospitals and other surgical facilities keep tissue allografts on hand for future use and suggested that the phrase ''pending scheduled'' be deleted from the exception. One comment projected that institutions would discontinue stocking tissue in order to avoid the registration requirement, leading to the denial to patients of appropriate implants. Another comment noted that thousands of hospitals and physician's offices store cells and tissue, and argued that registration could cause an unnecessary burden for facilities and FDA. One comment asserted that hospitals must follow the JCAHO guidelines for storage of tissues, monitoring of storage devices, and tracking of tissue use to provide for the safe storage of tissue. Another comment questioned whether physicians who receive sperm from a sperm bank and examine it for viability would be covered by the exception.

In response to many of these comments, we have deleted the phrase ''pending scheduled.'' The exception, codified at § 1271.15(d), now reads:

> You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores human cells or tissue solely for implantation, transplantation, infusion, or transfer within your facility.

As we noted in the preamble to the registration proposed rule (63 FR 26744 at 26748), this exception is intended only for end-user establishments; that is, establishments that do not recover, distribute, or otherwise manufacture human cells or tissue. Examples of such establishments might include some hospitals, dental offices, and physicians' offices. Physicians who do not recover sperm from donors but only receive sperm from a sperm bank would fall within the exception; examining the received sperm sample for viability would not be considered screening.

We believe that expanding this exception will ease the regulatory burden without posing public health concerns. To date, we have not become aware of problems with the types of facilities that will fall under the exception. However, should that situation change—e.g., should we encounter problems with tracking systems or learn of storage problems—we will consider narrowing the exception through rulemaking to bring these establishments within the scope of the regulation.

(Comment 35) One comment argued that registration should not be required for facilities collecting or using reproductive tissues from sexually intimate partners or close relatives. The comment strongly urged us to expand proposed § 1271.20(d) to include establishments that collect reproductive materials for use between sexually intimate partners or close relatives.

We agree with this comment, in part, and have added new paragraph (e) to the exceptions in § 1271.15. This exception is limited to establishments that recover reproductive materials for immediate use between sexually intimate partners. (By ''immediate use,'' we mean that the reproductive materials are used promptly enough that cryopreservation is not necessary and is not performed.) The exception is intended to cover an establishment that recovers semen for use in the artificial insemination of the donor's sexually intimate partner. We believe that this situation raises few new infectious disease concerns. For this reason, we are excepting these establishments from registering and from the other requirements that will be contained in part 1271. The exception does not extend to the recovery of cells or tissues from close relatives who are not sexually intimate partners, since an increased risk of communicable disease transmission exists in this situation.

E. Comments on Subpart B of Part 1271: Procedures for Registration and Listing

Many comments expressed general agreement with the proposed registration and listing procedures. One comment stated that the rule set forth a reasonable structure of requirements to be applied uniformly.

(Comment 36) One comment expressed concern that we might impose a registration fee.

We stated in the preamble to the registration proposed rule that we were evaluating our authority to assess a fee and the impacts of such a fee (63 FR 26744 at 26751). At this time, we have no plans to impose a registration fee.

(Comment 37) Comments opposed the proposed requirement in § 1271.21 for twice yearly reporting as excessive and supported annual listing updates instead. One comment noted that it is unlikely that the components processed by individual laboratories will change greatly over a 12-month period.

We disagree that the requirement for updating HCT/P lists is excessive. Establishments are required to update

their listings with information on changes that have occurred since the previously submitted list. These changes include the introduction of new HCT/P's, the discontinuation of HCT/P's, the reintroduction of previously discontinued HCT/P's, and material changes in information previously submitted. However, if no such change has occurred since the previously submitted list, the establishment is not required to submit an update.

Those establishments that must update their lists will likely find the task relatively simple. As discussed in section III.G of this document, Form FDA 3356 was designed with ease of completion in mind. Yet the information to be submitted on those updates is crucial if we are to keep abreast of developments in the cell and tissue industry. Without current information, we will be restricted in our ability to understand the industry and achieve our public health goals.

In setting up a unified registration system for all HCT/P's, we incorporated certain components from current registration and listing regulations for drugs and devices, such as the update requirements. By doing so, we made it possible for establishments that manufacture HCT/P's regulated as devices, drugs, and/or biological drugs to register and list their products with the agency using the same form as manufacturers of 361 HCT/P's. Thus, the requirement for updating is similar to the requirements in §§ 207.30 and 807.30 and is consistent with the requirements of section 510(j)(2) of the act.

We have rewritten the requirement for updates for greater clarity. Section 1271.21(c) now contains timeframes for updating. Section 1271.25(c) lists the changes that must be reported. The listed events to be reported have been corrected to reflect the type of information required to be included in the initial listing. Thus, for example, just as a listing includes the names of HCT/P's that an establishment recovers, processes, stores, labels, packages, distributes, or for which it performs donor screening or testing, so the updated listing would reflect any changes in the HCT/P's for which any of these activities are performed.

We have made an additional change to proposed § 1271.25(c), which would have required that copies of all contract service agreements be available at the time of inspection of the establishment. In order to avoid duplicating a similar requirement proposed in the GTP regulations, we have deleted the requirement from § 1271.25(c).

(Comment 38) We earlier stated that we were developing an electronic version of Form FDA 3356 (registration proposed rule, 63 FR 26750). One comment strongly supported these efforts and asserted that manufacturers should also be able to submit registration and listing information electronically.

We understand that it would be convenient to submit registration and listing information electronically over the Internet. We intend to rely on our experience in developing electronic submission capability in other areas (e.g., biological product deviations in manufacturing reports) to develop an electronic submission process for HCT/P registration and listing. When electronic submissions of Form FDA 3356 are possible, we will make an announcement to that effect.

(Comment 39) Two comments disagreed with the requirement proposed in § 1271.25(a)(4) for a statement affirming the truth and accuracy of all information in the registration and listing form. The comments argued that no similar requirement exists in the registration and listing regulations for drugs and devices, parts 207 and 807. The comments proposed that, if the requirement is maintained, the statement be qualified with a phrase such as ''to the best of my knowledge.''

To be of use, information submitted on the registration and listing form must be truthful and accurate. Moreover, the reporting official who completes and signs the form should be aware of the obligation to report truthfully and accurately. Although, as the comment points out, the registration and listing regulations for drugs and devices do not contain a similar statement, the act specifically prohibits the submission of false or misleading reports with respect to any device (section 301(q)(2) of the act (21 U.S.C. 331(q)(2)). Furthermore, a willfully false statement to a Federal agency is a criminal offense, and it is not uncommon for forms submitted to the agency to so note (18 U.S.C. 1001).

For these reasons, we are maintaining the requirement for a statement affirming the truth and accuracy of the information submitted on the registration and listing form. However, the reporting official may reasonably obtain the reported information from reliable sources rather than firsthand. For this reason, we believe it is reasonable to modify the required statement with the language ''to the best of my knowledge.'' We have made this change to the regulation and to the form.

(Comment 40) Two comments questioned the requirement proposed in § 1271.25(b) for a statement of whether each listed product meets the criteria set out in § 1271.10. One comment queried whether we plan to regard this statement as an admission that a product is or is not a 361 HCT/P. This comment suggested the addition of language consistent with that of other product registration and listing regulations clarifying that registration and listing under part 1271 does not constitute such an admission of product regulatory status. Both comments noted that only the statement is required, not an explanation or summary of why a product does or does not meet the criteria or which criteria are not met.

The categorization of HCT/P's as 361 HCT/P's or as drugs, devices, and/or biological products is a fundamental component of the new tiered, risk-based system. We are requiring this information for each HCT/P type to help us understand the HCT/P industry. Establishments need to know how their products are regulated in order to comply with appropriate requirements; therefore, the information required should be readily available. We understand that there may be instances where an establishment is unsure into which category its HCT/P falls; the establishment should contact the executive secretariat of the TRG in these situations. (For more information on the TRG, see CBER's website at http://www.fda.gov/cber/tissue/trg.htm.)

The requirement in § 1271.25(b) is for a statement only, not an explanation. The statement will inform the agency of the manufacturer's opinion, but will not be an ''admission'' with respect to how an HCT/P will be regulated. To be regulated solely under section 361 of the PHS Act and part 1271, an HCT/P must meet the criteria set forth under § 1271.10.

(Comment 41) Two comments requested that we clarify whether individual sizes or configurations of tissues should be listed separately, or instead under more general headings. One of these comments questioned whether a ''new'' product would include a new size of a product.

The information currently required on the registration and listing form is of a more general nature. Because the form does not ask for sizes, a new product would not include a new product size.

(Comment 42) One comment encouraged the use of standard product names for hematopoietic progenitor cell therapies in order to make product listing consistent.

We encourage the development of standard names. However, at this point we are requesting more general information on Form FDA 3356. In the

future, we may ask for more detailed information.

(Comment 43) One comment recommended that required listing information include, with respect to each listed type of tissue, the specific manufacturing activities conducted at each registered establishment.

To simplify the registration and listing form, we are not asking for specific manufacturing information for each product but for the establishment in general. If there is a need, we may possibly ask for more specific information in the future.

(Comment 44) One comment questioned whether the addition of an adjacent building with a different address would be considered a new location, requiring an amendment to registration under § 1271.26.

No. Adding an adjacent building would not require an amendment to registration.

(Comment 45) No comments were received on proposed § 1271.27, which deals with the assignment of a registration number. We wish, however, to note that establishments that are currently registered under the drug or device registration and listing requirements, and who would in the future register and list using the procedures in part 1271, when that part is fully effective, would keep the same registration number that was issued previously. Those establishments should provide that number to us when registering for the first time using the new procedures.

(Comment 46) One comment supported the release of registration and listing information under § 1271.37, but questioned how we would determine which information to disclose to the public.

The information submitted on Form FDA 3356 is not proprietary or confidential in nature and may be released to the public. Section 1271.37(a)(4) notes that the agency may also release all data or information that has already become a matter of public record. The agency will follow the procedures and requirements set out in 21 CFR part 20 to determine which information has become a matter of public record and may be released.

F. Comments on the Proposed Amendments to §§ 207.20 and 807.20

(Comment 47) No comments were submitted on the proposed amendments to §§ 207.20 and 807.20.

We have modified the language proposed for §§ 207.20(f) and 807.20(e) to clarify that establishments that manufacture HCT/P's regulated as devices, drugs, and/or biological products will register and list their products following the procedures in part 1271 instead of the procedures in parts 207 and 807. Thus, when this rule is effective for HCT/P's regulated as devices, drugs, and or biological products, these establishments will submit Form FDA 3356 according to the procedures set out in subpart B of part 1271, at the same time as other cell and tissue establishments, and will no longer have to submit other registration and listing forms. We have also renumbered proposed § 807.20(e) as § 807.20(d).

The effective date of §§ 207.20(f) and 807.20(d) is 2 years after the publication of this rule.

G. Comments on the Registration and Listing Form (Form FDA 3356)

We asked nine manufacturers to participate in a pilot study to evaluate FDA Form 3356 in draft form, as allowed by the Office of Management and Budget (OMB) before we finalized the paperwork burden analysis. The pilot study had two purposes: To evaluate the ease of use of Form FDA 3356, and to validate the data base software developed for FDA under contract. The pilot study took place in May 1998, and in August 1998 we submitted to the docket a summary of the results of the study.

Six of the participating establishments noted that the draft form was easy to use and required less than 1 hour to complete. Other comments on the form noted several areas of potential confusion. We have addressed many of these issues elsewhere in this document, in response to comments submitted to the docket. We have addressed other issues by modifying the instructions for completing the form.

We have made minimal changes to Form FDA 3356 and its instructions to conform to the revised requirements in part 1271, subpart B. We have not added any additional information requirements.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121) and under the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes the final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. OMB has determined that the final rule is a significant action as defined in Executive Order 12866.

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 one year. We have also determined that this rule will not result in aggregate expenditures for State, local, and tribal governments, or the private sector of $100 million in any one year (adjusted for inflation).

An analysis of available information suggests that costs to the entities most affected by this rule, including small entities, are not expected to 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 Action

This action is a first step in the regulation of the rapidly evolving industry of human cells and tissue. The entire industry has not been previously regulated under a single 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 human cells, tissues, and cellular and tissue-based products (HCT/P's) that are used by the industry. The rule will require all manufacturers of HCT/P's to register with the agency and to submit to the agency a list of their HCT/P's. Through registration and listing, FDA will be able to identify industry participants and the scope of the HCT/P's produced. 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 FDA oversight. This action is taken solely under the authority of section 361 of the PHS Act. Section 361 of the PHS

Act is also used as authority to amend parts 207 and 807 so that the registration and data bases for all human cells, tissues, and cellular and tissue-based products may be consolidated. FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the rule.

B. Small Entities Affected

This rule affects both establishments that currently register with FDA and submit product lists to the agency under applicable sections of the act (parts 207 and 807), and those establishments that are not presently required to register or list with the agency. FDA has structured registration and listing for HCT/P's to have a minimal impact on affected establishments. However, the agency anticipates that the impact will be greater for those establishments that do not currently register or list. Because the final rule is effective 75 days after publication of this document for those establishments currently regulated under part 1270, and is effective in 2 years for all other HCT/P establishments, the economic impact on the industry will be staggered.

The total number of establishments that are required to register and list under part 1271 in 2 years after the publication of this rule is estimated to be 1,225. The registration and listing initiative will, in part, help the agency obtain more accurate numbers of HCT/P's establishments. In calculating the burden, the agency has relied on information obtained from trade organizations related to the human cells, tissue, and cellular and tissue-based products industry, several of which also provided estimates of what portion of the industry their membership represented. Along with this information and from our own research, we determined that 65 manufacturers of human cells, tissue, and cellular and tissue-based products are registered with the agency as required by part 807. The agency also determined that one manufacturer of an HCT/P drug is registered as required by part 207

According to the U.S. Small Business Administration, a tissue bank is a small entity if it has annual revenues less than $5 million. FDA estimates that 110 tissue banks are involved in the manufacture of conventional tissue and that approximately 77.5 percent (or 85) of these banks are small entities. FDA estimates that there are 425 stem cell facilities (400 peripheral blood stem cell facilities and 25 cord blood facilities), and that all are small entities. FDA estimates that approximately 114 eye banks are currently operating in the United States, and industry experts estimate that virtually all facilities would be classified as small. FDA estimates that there are approximately 400 assisted reproductive technology (ART) facilities. This estimate is consistent with industry comments. Consultants estimate that two-thirds of all ART facilities (or 267 establishments) would be classified as small entities. In addition, the American Society of Reproductive Medicine (ASRM) has a 1996 list of approximately 110 sperm banks operating in the U.S. Information about sperm banks from a report by Eastern Research Group (ERG) indicates that 95 percent (or 105) of these sperm banks are small. Thus, approximately 996 (85 + 425 + 114 + 267 + 105) of all 1,225 establishments would be considered small entities. In addition, 66 establishments are currently regulated as drugs, devices, or biological products under parts 207 and 807. Approximately 90 percent of these (or 60 establishments) are small entities. Therefore, we estimate that a total 1,056 establishments (996 + 60) are small entities.

C. Nature of the Impact

The main cost in implementing this final rule is staff time, which we estimate to cost $38.00 per hour, based on 1997 Bureau of Labor Statistics estimates.

Out of a total 1,225 establishments affected by this rule, 66 HCT/P drug and device establishments currently submit registration and product listing information under parts 207 and 807. In the proposed rule, we incorrectly estimated both the time and the scope of annual information collection for these establishments. Our estimate inaccurately lumped the submission of all required information into one year and concluded that 2 hours would be needed annually to register and list initially, submit a subsequent annual registration, update HCT/P listings, and amend ownership or location information.

As proposed, however, this final rule requires that HCT/P drug and device manufacturers use a new, single form to register and list their HCT/P products. This rule does not impose any new registration or listing requirements for establishments regulated under parts 207 and 807. To avoid duplication, the rule provides HCT/P drug and device manufacturers a single, new form to replace the multiple forms currently required under parts 207 and 807. Therefore, we now estimate only the time needed to transition from the use of multiple forms to the use of the one form. Based on results from the pilot study described above in section III.G of this document, we estimate that establishments will need approximately 0.5 hour to transition to Form FDA 3356 at a one-time transition cost of approximately $19 [$38 x 0.5]. We estimate that the total impact for all 66 establishments will be approximately $1,254 [66 x $38 x 0.5].

For the 1,159 HCT/P manufacturers not regulated under parts 207 and 807, the costs are based upon the staff time needed to obtain the form, read the instructions, and complete and submit the form for the initial registration and HCP/T listing, subsequent annual registration, and, as needed, listing updates and location/ownership amendments. Based on the pilot study described above, FDA estimates that it will take an average of 0.75 hour of staff time per establishment for the initial submission. At $38.00 per hour of staff time, each establishment is expected to incur an initial one-time cost of approximately $28 [$38 x 0.75]. We estimate the total impact for all 1,159 establishments for the submission of initial registration and HCT/P listing to be approximately $33,032 [1,159 x $38 x 0.75].

After the initial registration, the final rule requires annual registration, which we estimate will take 0.5 hour to complete and submit to FDA. We estimate that the annual cost of these submissions will be approximately $22,021 [1,159 x $38 x 0.5] or $19 per establishment.

The final rule also requires HCT/P listing updates twice a year, a submission that is required only when a change has been made since the previous listing submission. FDA assumes that in any given year, 5 percent or 58 of the 1,159 establishments [1,159 x 0.05] will submit one listing. The listing update is estimated to take about 0.5 hours to complete and submit to FDA. We estimate that each establishment will incur an annual cost of approximately $19 [$38 x 0.5], for a total of $1,102 for all 58 establishments.

The rule also requires changes in ownership or location to be reported as an amendment within 5 days of such changes. FDA expects that this will be a rare event and that in any given year, no more than 5 percent or 58 of the 1,159 establishments [1,159 x 0.05] will change location or ownership and submit an amendment. This amendment is estimated to take 0.25 hours of staff time. We estimate that each establishment will incur a cost of approximately $10 [$38 x 0.25], totaling $580 for all 58 establishments.

In sum, we estimate the total annual for all submissions subsequent to the initial registration and listing (annual registration and, as needed, listing updates and location/ownership amendments) to be $23,702 [$22,021 + $1,101 + $580].

There are no specific educational or technical skills required to complete and submit the registration and listing form. Trained and qualified employees of an establishment who are involved with its operations generally complete similar activities.

This final rule is the first step in creating a tiered, risk-based regulatory scheme that will tailor the degree of scrutiny afforded to different HCT/P's to the risks associated with each of them. Through registration and listing, FDA will acquire the information needed to characterize the nature and extent of HCT/P's. This information will enable FDA to efficiently and effectively respond to emerging public health concerns related to human cells or tissue. Lists of industry members and their HCT/P's 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 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 will consider the use of electronic submissions (e-mail or Internet) and electronic signatures.

V. 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.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VII. The Paperwork Reduction Act of 1995

This final 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 (PRA) (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 initial one-time reporting burden and the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, completing and reviewing each collection of information.

Title: Establishment Registration and Listing Requirements for Human Cells, Tissues, and Cellular and Tissue-Based Products.

Description: The final rule requires establishments that recover, process, store, label, package, or distribute any human cell, tissue, and cellular and tissue-based product (HCT/P), or that perform donor screening or testing, to submit an initial establishment registration and HCT/P list to FDA. Subsequently, establishments must submit an annual update to their establishment registration. In addition, establishments are required to submit HCT/P list updates, if any, and amendments whenever an establishment changes ownership or locations. FDA provides a registration and listing form (Form FDA 3356) to facilitate the ease and speed of submissions. Form FDA 3356 is an approved information collection format under OMB control number 0910–0372. The approval expires July 31, 2001.

Description of Respondents: Establishments that recover, process, store, label, package, or distribute any human cells, tissue, and cellular and tissue-based product.

As required by section 3506(c)(2)(B) of the PRA, FDA provided an opportunity for public comment on May 14, 1998 (63 FR 26744), on the information collection requirements of the proposed rule.

Table 1 of this document lists the estimated one-time reporting burden for the initial establishment registration and HCT/P listing, which is required under § 1271.10(b). Section 1271.25(a) and (b) identify the initial establishment and HCT/P listing information required. Sections 207.20(f) and 807.20(d) require HCT/P establishments to use Form FDA 3356 for providing registration and listing information required under parts 207 and 807.

Table 2 of this document provides the estimate of the ongoing annual reporting burden for establishment registration. In addition, table 2 of this document sets out estimated reporting burdens for HCT/P listing updates and establishment location or ownership amendments that would occur during any given year. If there is no change to an HCT/P listing, establishment location or ownership, a submission is not required.

Sections 1271.21(b) and 1271.10(b) require the annual establishment registration by domestic and foreign HCT/P establishments that are solely regulated under section 361 of the PHS Act and this part.

Sections 1271.21(c)(ii), 1271.25(c), and 1271.10(b) require domestic and foreign HCT/P establishments to submit HCT/P listing updates only when an HCT/P is changed, added, or discontinued, and when there has been a material change to information submitted previously to the agency. If no change has occurred since the previous submission, an update is not required.

Sections 1271.26 and 1271.10(b) require domestic and foreign HCT/P establishments to submit an amendment, but only when the establishment makes a change in location or ownership.

Sections 207.20, 207.26, 207.30, 807.20, 807.26, and 807.30 already require establishments that manufacture drug or device products to submit initial establishment registration and product listing, as well as annual establishment registration, product listing updates, and location and ownership amendments. This final rule adds §§ 207.20(f) and 807.20(d), which require that manufacturers of HCT/P drugs and devices submit this registration and listing information using Form FDA 3356 instead of the multiple forms identified under parts 207 and 807. Therefore, these establishments will incur only a one-time burden to transition from the use of several forms to the use of one form (see table 1 above). This rule adds no new registration and listing requirements.

This final rule is implemented according to the staggered effective dates. Human tissues intended for transplantation that are currently regulated under section 361 of the PHS Act and part 1270 are required to register with the agency and list their HCT/P's within 5 days of the first effective date. The effective date for all other HCT/P's is 2 years after publication of this rule in the **Federal Register**, about which time we expect that the remaining subparts of part 1271 will become effective.

In the proposed rule, FDA underestimated the number of respondents. Based on additional information provided to FDA by industry representatives, trade organizations, and professional societies, we have revised our estimate of establishments to approximately 1,225 (i.e., approximately 110 conventional tissue, 114 eye tissue banks, 400 peripheral blood stem cells, 25 stem cell products from cord blood, 400 reproductive tissue, 110 sperm banks, and 66 licensed biological products and approved devices).

Our burden estimates for the annual frequency per response and average hours per response are based on institutional experience with comparable reporting provisions for drugs, including biological products, and devices, information from industry representatives and trade organizations, and data provided by the Eastern Research Group (ERG), a consulting firm hired by FDA to prepare an economic analysis of the potential economic impact on sperm banks and other reproductive tissue facilities.

In the final rule, we have separated the initial, one-time reporting requirements (table 1 of this document) from the subsequent ongoing annual establishment registration, HCT/P updates and amendment requirements (table 2 of this document).

Table 1 of this document provides the initial, one-time estimated burden for HCT/P establishment registration and HCT/P listing. This information may be submitted simultaneously on the same form, Form FDA 3356. We estimate that 0.75 hour of staff time will be needed for each initial submission. This estimate is based on a pilot program described above in section III.G of this document conducted to evaluate Form FDA 3356.

In table 1 of this document we also include the one-time burden for HCT/P drug and device manufacturers regulated under parts 207 and 807. Parts 207 and 807 require that drug and device manufacturers submit initial establishment registration and product listing, annual establishment registration, product listing updates, and location/ownership amendments. New §§ 207.20(f) and 807.20(d) change only the reporting format and require use of only one form, new Form FDA 3356, in place of the multiple forms currently required, i.e., Forms FDA–2656 and FDA–2657 for drug manufacturers, and Forms FDA–2891, FDA–2891(a), and FDA–2892 for device manufacturers. Therefore, the one-time reporting burden estimate for §§ 207.20(f) and 807.20(d) in table 1 of this document reflects only the time necessary to transition from the use of current multiple forms to the use of Form FDA 3356. In the proposed rule, we incorrectly included the time needed to submit the registration and listing information already required under parts 207 and 807. As revised here, the reporting burden under new §§ 207.20(f) and 807.20(d) reflects only the time necessary to transition from the use of current multiple forms to the use of Form FDA 3356.

Table 2 of this document shows more accurately than in the proposed rule that on-going annual registration, updates and amendments require 0.50 hour, while the initial submission requires on average 0.75 hour. In addition, table 2 of this document shows that the average hours per response is less for the HCT/P listing updates and location/ownership amendments, which are required only when a change is made, than for the annual registration, which must be submitted every year. In table 2 of this document, we also estimate that approximately 5 percent of the 1,159 establishments, or 58 establishments, will make changes to HCT/P's, location, or ownership in any one year after the initial registration and listing. Based on additional information from industry representatives and from our own experiences, we estimate that annual registration, HCT/P listing updates, and location/ownership amendments will require 0.5, 0.5, and 0.25 hours, respectively, as opposed to the full hour estimated for every establishment submission in the proposed rule. The greater precision afforded by this breakout shows that, despite the increased number of total estimated respondents, the estimated total burden hours is lower than in the proposed rule. In table 2 of this document, the total annual burden of 623 hours for ongoing reporting is slightly less than the initial, one-time reporting burden total of 902.25 hours in table 1 of this document.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED INITIAL (ONE–TIME) REPORTING BURDEN [1]

21 CFR	No. of respondents	Annual frequency per response	Total annual responses	Hours per response (average)	Total hours
207.20(f)	1	1	1	0.5	0.5
807.20(d)	65	1	65	0.5	32.50
Initial Registration and HCT/P Listing 1271.25(a), with 1271.25(b) and 1271.10(b)	1,159	1	1,159	0.75	869.25
TOTAL					902.25

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

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN [2]

21 CFR	No. of respondents	Annual frequency per response	Total annual responses	Hours per response (average)	Total hours
Annual Registration 1271.21(b) and 1271.10(b)	1,159	1	1,159	0.5	579.50
HCT/P Listing Update 1271.21(c), 1271.25(c), and 1271.10(b)	58	1	58	0.5	29.00

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN [2]—Continued

21 CFR	No. of respondents	Annual frequency per response	Total annual responses	Hours per response (average)	Total hours
Location/Ownership Amendment 1271.26 and 1271.10(b)	58	1	58	0.25	14.50
TOTAL					623

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

Individuals and organizations may submit comments on these burden estimates or on any other aspect of these information collection requirements, including suggestions for reducing the burden. Comments should be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research, Tissue Establishment Registration Coordinator (HFM–305), 1401 Rockville Pike, suite 200N, Rockville, MD 20852.

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

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Vice President's National Performance Review report, ''Reinventing the Regulation of Human Tissue,'' February 1997.

2. Schipper, R. F., D'Amaro, J., and Oudshoorn, M., ''The Probability of Finding a Suitable Related Donor for Bone Marrow Transplantation in Extended Families,'' *Blood*, 87:800–804, 1996.

3. Kaufman, R., ''A Generalized HLA Prediction Model for Related Donor Matches,'' *Bone Marrow Transplantation*, 17:1013–1020, 1996.

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 cells, Reporting and recordkeeping requirements, tissue-based products.

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

PART 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, 360, 360b, 371, 374; 42 U.S.C. 262, 264, 271.

2. Section 207.20 is amended by revising the heading and adding 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 cells, tissues, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter, that are regulated under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act must register and list those human cells, tissues, and cellular and tissue-based 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, instead of the procedures for registration and listing contained in this part, 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 revising the heading and adding paragraph (d) to read as follows:

§ 807.20 Who must register and submit a device list?

* * * * *

(d) Owners and operators of establishments or persons engaged in the recovery, screening, testing, processing, storage, or distribution of human cells, tissues, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter, that are regulated under the Federal Food, Drug, and Cosmetic Act must register and list those human cells, tissues, and cellular and tissue-based 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, instead of the procedures for registration and listing contained in this part, except that the additional listing information requirements of § 807.31 remain applicable.

5. Part 1271 is added to read as follows:

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

Subpart A—General Provisions

Sec.

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

Subpart A—General Provisions

§ 1271.1 What are the purpose and scope of this part?

(a) *Purpose.* The purpose of this part, in conjunction with §§ 207.20(f), 210.1(c), 210.2, 807.20(d), and 820.1(a) of this chapter, is to create a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/P's) and to establish donor-suitability, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's.

(b) *Scope.* (1) If you are an establishment that manufactures HCT/P's that are regulated solely under the authority of section 361 of the Public Health Service Act (the PHS Act), this part requires you to register and list your HCT/P's with the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research and to comply with the other requirements contained in this part, whether or not the HCT/P enters into interstate commerce. Those HCT/P's that are regulated solely under the authority of section 361 of the PHS Act are described in § 1271.10.

(2) If you are an establishment that manufactures HCT/P's that are regulated as drugs, devices and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act, §§ 207.20(f) and 807.20(d) of this chapter require you to register and list your HCT/P's following the procedures in subpart B of this part. Sections 210.1(c), 210.2, 211.1(b), and 820.1(a) of this chapter require you to comply with the donor-suitability procedures in subpart C of this part and the current good tissue practice procedures in subpart D of this part, in addition to all other applicable regulations.

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

The following definitions apply only to this part:

(a) *Autologous use* means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.

(b) *Establishment* means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products. ''Establishment'' includes:

(1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cells, tissues, and cellular and tissue-based products; and

(2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products.

(c) *Homologous use* means the replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

(d)(1) *Human cells, tissues, or cellular or tissue-based products (HCT/P's)* means any human tissue derived from a human body and intended for transplantation into another human, as defined under § 1270.3(j). Examples of HCT/P's include, but are not limited to, bone, ligament, skin, and cornea.

(2) *Human cells, tissues, or cellular or tissue-based products (HCT/P's)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/P's include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/P's:

(i) Vascularized human organs for transplantation;

(ii) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(iii) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;

(iv) Minimally manipulated bone marrow for homologous use and not combined with a drug or a device (except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

(v) Ancillary products used in the manufacture of HCT/P;

(vi) Cells, tissues, and organs derived from animals other than humans; and

(vii) In vitro diagnostic products as defined in § 809.3(a) of this chapter.

(e) *Manufacture means*, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

(f) *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 or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

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

§ 1271.10 Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cell or tissue component with a drug or a device, except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(*a*) Is for autologous use;

(*b*) Is for allogeneic use in a first-degree or second-degree blood relative; or

(*c*) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.

§ 1271.15 Are there any exceptions from the requirements of this part?

(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

(e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.

§ 1271.20 If my HCT/P's do not meet the criteria in § 1271.10, and I do not qualify for any of the exceptions in § 1271.15, what regulations apply?

If you are an establishment that manufactures an HCT/P that does not meet the criteria set out in § 1271.10(a), and you do not qualify for any of the exceptions in § 1271.15, your HCT/P will be regulated as a drug, device, and/or biological product under the act and/or section 351 of the PHS Act, and applicable regulations in title 21, chapter I. Applicable regulations include, but are not limited to, §§ 207.20(f), 210.1(c), 210.2, 211.1(b), 807.20(d), and 820.1(a) of this chapter, which require you to follow the procedures in subparts B, C, and D of this part.

Subpart B—Procedures for Registration and Listing

§ 1271.21 When do I register, submit an HCT/P list, and submit updates?

(a) You must register and submit a list of every HCT/P that your establishment manufactures within 5 days after beginning operations or within 30 days of the effective date of this regulation, whichever is later.

(b) You must update your establishment registration annually in December, except as required by § 1271.26. You may accomplish your annual registration in conjunction with updating your HCT/P list under paragraph (c) of this section.

(c)(i) If no change described in § 1271.25(c) has occurred since youpreviously submitted an HCT/P list, you are not required to update your listing.

(ii) If a change described in § 1271.25(c) has occurred, you must update your HCT/P listing with the new information:

(*a*) At the time of the change, or

(*b*) Each June or December, whichever month occurs first after the change.

§ 1271.22 How and where do I register and submit an HCT/P list?

(a) You must use Form FDA 3356 for:

(i) Establishment registration,

(ii) HCT/P listings, and

(iii) Updates of registration and HCT/P listing.

(b) You may obtain Form FDA 3356:

(i) By writing to the Center for Biologics Evaluation and Research (HFM–305), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, Attention: Tissue Establishment Registration Coordinator;

(ii) By contacting any Food and Drug Administration district office;

(iii) By calling the CBER Voice Information System at 1–800–835–4709 or 301–827–-1800;

(iv) By calling the Fax Information System at 1–888–CBER–FAX or 301–827–3844; or

(v) By connecting to http://forms.psc.gov/forms/FDA/fda.html on the Internet.

(c)(i) You may submit Form FDA 3356 to the Center for BiologicsEvaluation and Research (HFM–305), Food and Drug Administration, 1401 Rockville, Pike, Rockville, MD 20852–1448, Attention: Tissue Establishment Registration Coordinator; or

(ii) You may submit Form FDA 3356 electronically in accordance with the instructions provided with the form.

§ 1271.25 What information is required for establishment registration and HCT/P listing?

(a) Your establishment registration Form FDA 3356 must 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 dated signature by the reporting official affirming that all information contained in the establishment registration and HCT/P listing form is true and accurate, to the best of his or her knowledge.

(b) Your HCT/P listing must include all HCT/P's (including the established name and the proprietary name) that you recover, process, store, label, package, distribute, or for which you perform donor screening or testing. You must also state whether each HCT/P meets the criteria set out in § 1271.10.

(c) Your HCT/P listing update must include:

(1) A list of each HCT/P that you have begun recovering, processing, storing, labeling, packaging, distributing, or for which you have begun donor screening or testing, that has not been included in any list previously submitted. You must provide all of the information required by § 1271.25(b) for each new HCT/P.

(2) A list of each HCT/P formerly listed in accordance with § 1271.21(a) for which you have discontinued recovery, processing, storage, labeling, packaging, distribution, or donor screening or testing, including for each HCT/P so listed, the identity by established name and proprietary name, and the date of discontinuance. We request but do not require that you include the reason for discontinuance with this information.

(3) A list of each HCT/P for which a notice of discontinuance was submitted under paragraph (c)(2) of this section and for which you have resumed recovery, processing, storage, labeling, packaging, distribution, or donor screening or testing, 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.

(4) Any material change in any information previously submitted. Material changes include any change in information submitted on Form FDA 3356, such as whether the HCT/P meets the criteria set out in § 1271.10.

§ 1271.26 When must I amend my establishment registration?

If the ownership or location of your establishment changes, you must submit an amendment to registration within 5 days of the change.

§ 1271.27 Will FDA assign me a registration number?

(a) FDA will assign each location a permanent registration number.

(b) FDA acceptance of an establishment registration and HCT/P listing form does not constitute a determination that an establishment is in compliance with applicable rules and regulations or that the HCT/P is licensed or approved by FDA.

§ 1271.37 Will establishment registrations and HCT/P listings be available for inspection, and how do I request information on registrations and listings?

(a) A copy of the Form FDA 3356 filed by each establishment will be available for public 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 HCT/P requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(1) A list of all HCT/P's;

(2) A list of all HCT/P's manufactured by each establishment;

(3) A list of all HCT/P's discontinued; and

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

(b) You should direct your requests for information regarding HCT/P establishment registrations and HCT/P listings 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: January 2, 2001.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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DEPARTMENT OF THE TREASURY

Bureau of Alcohol, Tobacco and Firearms

27 CFR Parts 17 and 18

[T.D. ATF–436]

RIN 1512–AB99

Delegation of Authority for Parts 17 and 18

AGENCY: Bureau of Alcohol, Tobacco and Firearms (ATF), Treasury.

ACTION: Treasury decision, final rule.

SUMMARY: Authority delegation. This final rule places most ATF authorities contained in parts 17 and 18, title 27 Code of Federal Regulations (CFR), with the ''appropriate ATF officer'' and requires that persons file documents required by parts 17 and 18, title 27 Code of Federal Regulations (CFR), with the ''appropriate ATF officer'' or in accordance with the instructions on the ATF form. Also, this final rule removes the definitions of, and references to, specific officers subordinate to the Director. Concurrently with this Treasury Decision, ATF Order 1130.13 is being published. Through this order, the Director has delegated most of the authorities in 27 CFR parts 17 and 18 to the appropriate ATF officers and specified the ATF officers with whom applications, notices and other reports, which are not ATF forms, are filed.

EFFECTIVE DATE: January 19, 2001.

FOR FURTHER INFORMATION CONTACT: Robert Ruhf, Regulations Division, Bureau of Alcohol, Tobacco and Firearms, 650 Massachusetts Avenue NW, Washington, DC 20226 (202–927–8210).

SUPPLEMENTARY INFORMATION:

Background

Pursuant to Treasury Decision 120–01 (formerly 221), dated June 6, 1972, the Secretary of the Treasury delegated to the Director of the Bureau of Alcohol, Tobacco and Firearms (ATF), the authority to enforce, among other laws, the provisions of chapter 51 of the Internal Revenue Code of 1986 (IRC). The Director has subsequently redelegated certain of these authorities to appropriate subordinate officers by way of various means, including by regulation, ATF delegation orders, regional directives, or similar delegation documents. As a result, to ascertain what particular officer is authorized to perform a particular function under chapter 51, each of these various delegation instruments must be consulted. Similarly, each time a delegation of authority is revoked or redelegated, each of the delegation documents must be reviewed and amended as necessary.

ATF has determined that this multiplicity of delegation instruments complicates and hinders the task of determining which ATF officer is authorized to perform a particular function. ATF also believes these multiple delegation instruments exacerbate the administrative burden associated with maintaining up-to-date delegations, resulting in an undue delay in reflecting current authorities.

Accordingly, in this final rule, the Director of ATF is rescinding all authorities of the Director in parts 17 and 18 which were previously delegated to a specified ATF officer and placing all authorities of the Director with the ''appropriate ATF officer.'' Along with this final rule, ATF is publishing ATF Order 1130.13, Delegation Order—Delegation of the Director's Authorities in parts 17 and 18, in which certain of these authorities are then delegated down to the appropriate organizational level. The effect of these changes is to consolidate all delegations of authority in parts 17 and 18 into one delegation instrument. This action both simplifies the process for determining what ATF officer is authorized to perform a particular function and facilitates the updating of delegations in the event of a change in delegation or in the event of a restructuring. As a result, delegations of authority will be reflected in a more timely and user-friendly manner.

In addition to the above, this final rule also eliminates all references in the regulations which identify the ATF officer with whom an ATF form is filed. Thus, in lieu of identifying the authorized officer in the regulations, the form itself will indicate the officer with whom it shall be filed. Similarly, this final rule also amends parts 17 and 18 to provide that documents other than ATF forms (such as letterhead applications, notices and reports) will be filed with the ''appropriate ATF officer.'' The ''appropriate ATF officer'' is the Director's delegate and will be identified in the accompanying ATF Order (ATF Order 1130.13, Delegation Order—Delegation of the Director's