and faulty packaging are all examples of improper practices that could lead to a product capable of transmitting disease to its recipient. Similarly, as noted in the proposed approach document, improper handling of a human cellular or tissue-based product can lead to bacterial contamination of the product or to cross-contamination between products.

In addition to the direct transmission of communicable disease agents by human cellular and tissue-based products to their recipients, the agency is also concerned about the spread of communicable disease through the use of products whose function or integrity have been impaired. When a product does not work in a patient because it has not been manufactured properly, the risk of introducing, transmitting, or spreading a communicable disease is increased each time a procedure is repeated for at least two reasons: (1) Despite the best controls, there is a risk, albeit smaller than without controls, of communicable disease transmission, and (2) a procedure for transfer or transplant can carry an independent risk of communicable disease transmission. For example, use of a product whose function or integrity may have been compromised could create a circumstance that increases a patient's need for an additional transfer or transplant attempt. A repeat surgical procedure necessitated by the damaged product would further expose the patient to the additional communicable disease risks inherent in any such procedure. Moreover, a patient in a weakened state from the first unsuccessful procedure is at greater risk of contracting a communicable disease by experiencing a repeat procedure. Therefore, the agency considers that requirements aimed at maintaining product function and integrity are necessary, and thus may be issued under section 361 of the PHS Act.

The proposed CGTP regulations would govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products. CGTP requirements are a fundamental component of FDA's risk-based approach to regulating human cellular and tissue-based products. Products that the agency is proposing to regulate solely under section 361 of the PHS Act and proposed part 1271, would be subject to less rigorous agency oversight than products also regulated under the act and/or section 351 of the PHS Act. By requiring that 361 products be manufactured in compliance with CGTP, in combination with the other proposed requirements in part 1271, the agency can be assured that 361 products are subject to sufficient regulatory controls to protect the public health.

FDA is proposing that the CGTP regulations would supplement, but not supersede, the current good manufacturing practice (CGMP) and quality system (QS) regulations applicable to drugs and devices in parts 210, 211, and 820 (21 CFR parts 210, 211, and 820). Under the proposed rule, human cellular and tissue-based products regulated as biological drugs under the act and section 351 of the PHS Act, or as devices under the act, would have to be manufactured in accordance with CGTP, in addition to existing requirements. Thus, in keeping with the plan outlined in the proposed approach document, those products regulated as biological drugs or devices would be subject to more comprehensive regulation of manufacturing than the 361 products.

In the donor-suitability proposed rule, the agency proposed to amend the existing CGMP regulations for drugs and the QS requirements for devices to incorporate the testing and screening provisions of proposed part 1271, subpart C. At that time, in order to obviate the need for further revisions, the agency also proposed to amend those sections to incorporate the current good tissue practice procedures of proposed part 1271 subpart D. In amending the CGMP and QS regulations, FDA is relying both on the authority provided by section 361 of the PHS Act to make regulations to prevent the spread of communicable disease, and on its authority under the act to issue CGMP regulations (section 301(a)(2)(B) and (h) of the act) (21 U.S.C. 351(a)(2)(B) and (h)), section 520(f)(1) of the act (360j(f)(1)); section 701 of the act (21 U.S.C. 371)).

Under proposed 21 CFR 210.1(c), the manufacturer of a human cellular or tissue-based product regulated as a drug or biological drug would be required to comply with the CGTP procedures in part 1271, subpart D (donor suitability proposed rule, (64 FR 52696 at 52699 and 52719)). Likewise, under proposed 21 CFR 820.1, the manufacturer of a human cellular or tissue-based product regulated as a device would be required to comply with the same procedures (donor suitability proposed rule (64 FR 52696 at 52699 and 52719)). If the manufacturer failed to follow the CGMP requirements, including the good tissue practice procedures in part 1271, the product would be adulterated under section 501(a)(2)(B) of the act.

FDA is also relying on its authority under section 361 of the PHS Act to propose several reporting, labeling, inspection, and enforcement provisions. Because products regulated under the act and/or section 351 of the PHS Act, are subject to similar regulation requirements, these provisions would apply only to 361 products. Proposed subpart E of part 1271 contains regulations on reporting and labeling pertaining to 361 products and is discussed in section III of this document. Proposed subpart F of part 1271 contains inspection and enforcement provisions also applicable only to 361 products; the relevant discussion appears in section IV of this document.

II. Summary of the Proposed CGTP Regulations

The regulations being proposed would require manufacturers of human cellular and tissue-based products to follow CGTP, which includes proper handling, processing, storage, and labeling of human cellular and tissue-based products, recordkeeping, and the establishment of a quality program. The proposed CGTP regulations are designed to address issues common to all human cellular and tissue-based products, and so are intentionally broad in scope. The agency anticipates that, as it implements the new regulations, there may be additional need for discussion, through public meetings, public hearings, or guidance, of how these general regulations would apply to specific types of products. In addition, there may be specific elements of these proposed requirements that some readers may not consider appropriate to general application. The agency welcomes comments that will assist it in achieving the proper balance between generality and specificity in these regulations.

A. General Provisions (Proposed §§ 1271.150 and 1271.155)

Proposed § 1271.150 contains general provisions intended to aid in the interpretation of the requirements contained in subparts C and D of part 1271. Proposed § 1271.155 sets out the procedures for obtaining an exemption or variance from one or more of these requirements.

1. Current Good Tissue Practice (Proposed § 1271.150(a))

Proposed § 1271.150(a) states that CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products. CGTP requirements are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by helping to

ensure that: (1) The products do not contain relevant communicable disease agents; (2) they are not contaminated during the manufacturing process; and (3) the function and integrity of the products are not impaired through improper manufacturing, all of which could lead to circumstances that increase the risk of communicable disease transmission. "Manufacture" as defined in the registration proposed rule, includes, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product, and the screening and testing of a cell or tissue donor (proposed § 1271.3(f), 63 FR 26744 at 26754.) The definition of "human cellular or tissue-based product" as revised in the donor suitability proposed rule, is intended to cover such products at all stages of their manufacture, from recovery through distribution (see proposed § 1271.3(e) (64 FR 52696 at 52719). For a human cellular or tissue-based product to be manufactured properly, CGTP must be followed in each step of the manufacturing process.

The word "current" is included in the term "current good tissue practice" because the agency recognizes that appropriate practices may change over time, as research is conducted and new manufacturing methods are developed. These regulations are not intended to require that practices considered current at the time of issuance of the final regulations be maintained indefinitely; instead, the obligation on an establishment is to maintain up-to-date practices over time. Recognizing that improved manufacturing techniques may be developed, the agency has generally refrained in these proposed regulations from requiring specific procedures, such as particular processing methods or storage temperatures. Instead, the proposed regulations set out general objectives. This approach not only allows for new developments, but also affords establishments flexibility in developing procedures that are both appropriate to their particular operations and that comply with the regulations.

The proposed requirements are based on current good industry practice and are intended to address what the agency considers important minimum criteria for the manufacture of these products. In developing these regulations, the agency has reviewed several sets of industry standards, including those issued by the American Association of Tissue Banks (AATB) and by the Eye Bank Association of America (EBAA). The agency expects that some establishments will need to make only small changes in their operations to achieve compliance. Other establishments may find that complying with the new requirements entails revising certain procedures and recordkeeping practices, but few operational changes. Another group of establishments—for example, those that have not previously been subject to regulation and that do not belong to any standard-setting or accrediting organization—may need to revise their procedures more completely, in order to bring them into compliance with these regulations and industry practice.

Proposed § 1271.150(a) states that CGTP requirements are set forth in subparts C and D of part 1271. The CGTP provisions specifically governing donor suitability, including donor testing and screening, are set out separately in subpart C of part 1271. The agency notes that § 1271.90 contains exceptions from required testing and screening for two types of human cellular and tissue-based product: Banked cells and tissues for autologous use, and reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use (64 FR 52696 at 52723). (Donor testing and screening are recommended, however.) The agency specifically notes that the exceptions in § 1271.90 apply only to subpart C of part 1271 and do not extend to the provisions of subpart D of part 1271. Because the safety concerns addressed by the proposed CGTP requirements apply to all human cellular and tissue-based products, no exceptions are being proposed for any particular category of product. Thus, banked cells and tissues for autologous use, and reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use, would be subject to the CGTP requirements in subpart D of part 1271.

2. Compliance With Applicable Requirements (Proposed § 1271.150(b))

FDA recognizes that several establishments may be involved in the manufacture of a single human cellular or tissue-based product. For example, one establishment may recover tissue from a cadaver, another establishment may make the donor-suitability determination, a third may process the tissue, and a fourth may distribute the product. The agency has taken care, in designing these proposed regulations, to reflect the fact that manufacturing roles might be divided up in a variety of possible ways. Thus, under proposed § 1271.150(b), an establishment that engages in only some operations subject to the regulations in subparts C and D of part 1271 need only comply with those requirements applicable to the operations in which it engages. Under § 1271.150(b), an establishment that does not process cells or tissue would not be obligated to establish and maintain process controls under proposed § 1271.220. However, an establishment that engages another establishment, under a contract, agreement, or other arrangement, to perform any step in the manufacturing process, would be responsible for ensuring that the work is performed in compliance with the requirements in subparts C and D of part 1271. One method of accomplishing this might be by performing periodic audits.

Given that the steps in manufacturing a single human cellular or tissue-based product may be carried out by several establishments, FDA considers it essential that additional safeguards be established to ensure compliance with regulatory requirements throughout the manufacturing process. The agency has considered various ways of allocating regulatory responsibilities among the establishments involved in manufacturing a human cellular or tissue-based product. The agency seeks to permit establishments to maintain flexibility in sharing manufacturing responsibilities, while ensuring that products made available for release maintain their function and integrity, are not contaminated, and do not contain communicable disease agents.

The agency first considered assigning overall responsibility for ensuring that a human cellular and tissue-based product is manufactured in compliance with all applicable regulations to the establishment that determines donor suitability. However, the agency recognized that the role this establishment plays in the manufacture of a human cellular or tissue-based product occurs early in the sequence of manufacturing events. As a practical matter, the establishment that determines donor suitability might not be able to ensure that later manufacturing steps, such as processing and labeling, are performed in compliance with the regulations. A more pragmatic approach would be to assign responsibility to the establishment that makes a product available for distribution.

Another option would be to permit the establishments engaged in the manufacturing process to decide among themselves which party bears ultimate responsibility for the product. However, the agency is concerned that, under this approach, there would be occasions when no establishment would step forward as the one ultimately responsible, and that as a consequence

compliance with certain requirements might not be accomplished. As a result, products might be released that pose a risk of transmitting communicable disease or otherwise increasing the risk of disease transmission. For the same reasons, FDA has rejected the idea that designating a responsible establishment is unnecessary.

The agency has also considered a "cascading" set of responsibilities. Under this approach, an establishment would be responsible for ensuring that its own operations comply with applicable requirements, and also would bear the burden of proof that operations performed by other establishments prior to its receipt of the cells or tissue were performed in compliance with applicable requirements.

After considering the unique nature of the cell and tissue industry, and each of the above options, the agency has tentatively concluded that the best approach is to assign ultimate responsibility for the product to the establishment that is responsible for making the product available for distribution. This is consistent with the proposed approach document, which stated that "[t]he establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material." Thus, proposed § 1271.150(b) states that the establishment that determines that a product meets release criteria and makes the product available for distribution, whether or not that establishment is the actual distributor, is responsible for ensuring that the product has been manufactured in compliance with the requirements of subpart C and D of part 1271 and any other applicable requirements.

The agency specifically requests comments on the allocation of overall manufacturing responsibility. Examples of industry arrangements currently in existence would be particularly useful to the agency in evaluating the comments on these proposed regulations.

3. Compliance With Parts 210, 211, and 820

The proposed CGTP regulations are similar to the CGMP requirements applicable to drugs and the QS requirements for devices. However, the CGMP and QS regulations do not contain provisions specifically intended to prevent the spread of communicable disease. In contrast, the purpose of the proposed CGTP regulations is limited to preventing circumstances that increase the risk of introduction, transmission, and spread of communicable disease; the proposed regulations are therefore less extensive in scope than the CGMP and QS regulations.

Proposed § 1271.150(c) states that, with respect to human cellular and tissue-based products regulated as biological drugs or as devices, the proposed CGTP procedures will supplement, not supersede, the CGMP and QS requirements. Proposed § 1271.150(c) states that, in the event that it is impossible to comply with all applicable regulations, the regulations specifically applicable to the biological drug or device in question shall supersede the more general.

4. "Where Appropriate"

Several of the requirements contained in part 1271, subpart D, are qualified by the term "where appropriate," which as explained in proposed § 1271.150(d), are considered to be appropriate, and must be followed, unless an establishment can justify otherwise, and maintains documentation of that justification. Under proposed § 1271.150(d), a requirement is "appropriate" if nonimplementation could reasonably be expected to result in the: (1) Product's not meeting its specified requirements related to preventing the introduction, transmission, and spread of communicable disease agents and diseases; or (2) manufacturer's inability to carry out any necessary corrective action.

5. Exemptions and Alternatives (Proposed § 1271.155)

FDA recognizes the possibility that, as technology and scientific knowledge advance, new methods may be developed that could be used in the manufacture of human cellular and tissue-based products, or other unanticipated circumstances may arise that warrant a departure from an approach detailed in the regulations. Some of these technical developments may not be consistent with the terms of the donor-suitability and CGTP regulations, although the purpose of those regulations might be satisfied. In order to provide establishments with flexibility, and to ensure that the agency may respond appropriately to improved technologies and increased scientific knowledge, the agency proposes that establishments may apply for exemptions or alternatives from the regulatory requirements contained in subparts C and D of part 1271.

Proposed § 1271.155 sets out the procedures for obtaining an exemption or alternative from a requirement in subpart C of part 1271, pertaining to donor suitability, or in subpart D of part 1271, pertaining to CGTP. Under proposed § 1271.155, an establishment could demonstrate to the agency that it should be exempted from an otherwise applicable regulatory requirement or permitted to satisfy the purpose of the requirement in an alternative manner. A request for an exemption or alternative would need to be accompanied by supporting documentation, including all relevant valid scientific data. Requests would be made in writing or electronically, except that in limited circumstances (e.g., emergencies) a request might be made and granted orally, with a written request and acknowledgment of approval to follow.

Under proposed § 1271.155(c), the Director of the Center for Biologics Evaluation and Research (CBER) could grant an exemption or alternative if he or she found that doing so would be consistent with the goals of preventing circumstances that increase the risk of the introduction, transmission, and spread of communicable disease. In addition, an exemption or alternative would be conditioned on a finding by the Director that the information submitted justified an exemption or that the proposed alternative satisfied the purpose of the requirement. An establishment that requested an exemption or alternative could not begin operating under its terms until the exemption or alternative had been granted. Some exemptions or alternatives might have expiration dates, in which case an extension could be requested. An establishment operating under the terms of an exemption or alternative would be required to maintain documentation that the exemption or alternative had been granted, and of the date on which the establishment began operating under the terms of the exemption or alternative.

B. Definitions (Proposed § 1271.3)

Definitions pertinent to part 1271 will be contained in subpart A, in § 1271.3. In the registration proposed rule, FDA set out defined terms in paragraphs (a) through (h) of § 1271.3. In the donor-suitability proposed rule, further definitions were proposed, to be contained in § 1271.3(i) through (ee), and the proposed definition of human cellular or tissue-based product in paragraph (e) was revised.

Now, the agency is proposing new paragraphs (ff) through (tt) in § 1271.3. These new definitions are discussed below, when the requirements to which the defined terms relate are discussed.

C. Quality Program (Proposed § 1271.160)

Any establishment that manufactures human cellular or tissue-based products

needs to have in place a method of ensuring that its manufacturing processes are performed properly and in compliance with applicable regulations. For devices, such a program is called a "quality system" (§ 820.1 *et seq.*). In these regulations, FDA is proposing to use "quality program" to refer to the set of activities, including management review, training, audits, and corrective and preventive actions, that represent a commitment on the part of an establishment's management to the quality of its products. FDA proposes to define "quality program" in § 1271.3(oo) as "an organization's comprehensive system for manufacturing and tracking human cellular and tissue-based products. This program includes preventing, detecting, and correcting deficiencies that may lead to circumstances that increase the risk of the introduction, transmission, or spread of communicable disease."

Proposed § 1271.160 would require an establishment that performs any step in the manufacture of human cellular and tissue-based products to establish and maintain a quality program that is appropriate for the specific human cellular and tissue-based products manufactured and the manufacturing steps performed and that meets the requirements of this part. With proposed § 1271.160, FDA intends to require that a quality program perform certain basic functions, but also intends to provide each establishment with flexibility to devise a program appropriate to its particular activities and characteristics. Thus, FDA expects that quality programs may differ from establishment to establishment, depending on the size of the establishment and the type of manufacturing performed, among other factors. A smaller company that performs limited manufacturing steps might have a less complex quality program than a larger establishment that processes a variety of products.

Some establishments may currently have in place quality programs that would meet the requirements of proposed § 1271.160. An establishment that manufactures human cellular and tissue-based products regulated as devices would likely find it unnecessary to make major changes to its quality system established in compliance with § 820.5 in order to comply with proposed § 1271.160. Such an establishment would not need to maintain both a QS and a separate quality program.

The functions of a quality program, as listed in proposed § 1271.160(b), include but are not limited to: (1) Ensuring that required procedures are established and maintained; (2) ensuring the appropriate analysis and sharing of information that could affect the integrity and function of a human cellular or tissue-based product, possible contamination of the product, or the potential transmission of communicable disease by the product; (3) ensuring that appropriate corrective actions are taken and documented; (4) ensuring the proper training and education of personnel; (5) establishing and maintaining appropriate monitoring systems; (6) establishing and maintaining a system for maintaining records; (7) investigating and documenting product deviations and making certain required reports; and (8) conducting evaluations, investigations, audits, and other actions necessary to ensure compliance with the regulations.

Proposed § 1271.160(b)(2) would specifically require procedures to be established for sharing and receiving information that could affect the integrity and function of a human cellular or tissue-based product, the possible contamination of the product, or the potential transmission of communicable disease by the product. This would include information on testing or screening results that could make a donor unsuitable; such information would need to be shared with other establishments that are known to have recovered cells or tissue from the same donor. An establishment would also need procedures in place in order to respond appropriately (through investigation, evaluation, possible recall, reporting, etc.) if it received any such information from another establishment.

Proposed § 1271.160(b)(7) would require establishments to investigate and document all product deviations in manufacturing. The term "product deviation" is defined in proposed § 1271.3(kk) as "an event that represents a deviation from current good tissue practice, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from a human cellular or tissue-based product to a recipient, may lead to product contamination, or may adversely affect the function or integrity of the product." Investigation would be required to include a review and evaluation of the product deviation in manufacturing, the efforts made to determine the cause, and the implementation of corrective action designed to address the event and prevent its recurrence.

Certain product deviations in manufacturing would be required to be reported. The proposed requirement, applicable to distributed 361 products, for reporting product deviations in manufacturing that could lead to adverse reactions is discussed below in section III of this document. Certain product variations, referred to currently as errors and accidents, involving human cellular and tissue-based products regulated as biological drugs are required to be reported under 21 CFR 600.14 (currently undergoing revisions; see 62 FR 49642, September 23, 1997). In addition, each establishment would be required to perform a periodic review and analysis of all investigations of product deviations in manufacturing, at least once each year, for the purpose of identifying trends and adopting appropriate corrective and preventive measures. Section 1271.160(b)(7) specifies that this analysis shall be available for review upon inspection and for submission to FDA upon request.

Under proposed § 1271.160(c), one or more designated persons shall have authority over the quality program, and this person shall report to management at least once a year on the performance of the quality program. However, more frequent reports may be necessary in order to keep management informed of the status of the program.

Audits are an important component of a quality program. Under proposed § 1271.160(d), a comprehensive quality audit of all activities would be required at least once a year. FDA proposes to define "quality audit" in proposed § 1271.3(nn), as "a documented, independent inspection and review of an establishment's activities, including manufacturing and tracking, performed according to procedures, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review." In addition to the annual quality audit, special audits would be performed as necessary to ensure that quality program objectives are achieved.

Proposed § 1271.160(e) covers the use of computers or automated data processing systems used as part of the quality program, as part of manufacturing, or for maintaining manufacturing data or records. An establishment using such a computer or automated system would be required to validate the computer software for its intended use according to an established protocol, as well as all software changes. Validation and results would be required to be documented. The agency proposes to define

"validation" in proposed § 1271.3(rr) as "confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled * * *".

D. Organization and Personnel (Proposed § 1271.170)

Proposed § 1271.170 sets out general requirements for the organization and personnel of establishments that manufacture human cellular and tissue-based products. Under this section, each establishment would be required to maintain an adequate organizational structure and sufficient personnel to ensure that the requirements of part 1271 are met. Moreover, an establishment would need to have sufficient personnel with the necessary education and experience, or combination thereof, to assure competent performance of their assigned functions.

Under proposed § 1271.170, personnel would only be permitted to perform those activities for which they are qualified. Training of personnel to perform their assigned responsibilities adequately would be required, as would any necessary retraining. Because of the particular risks addressed by the requirements of part 1271, the agency is proposing to require that personnel be educated about possible consequences of improperly performing their duties; e.g., the risk that an improperly handled product could cause harm to the product's recipient, by transmitting a communicable disease or by failing to function adequately. A record of the education, experience, training, and retraining would need to be maintained for all personnel.

E. Procedures (Proposed § 1271.180)

Under proposed § 1271.180, each establishment would be required to establish and maintain procedures for all significant steps that it performs in the manufacture of human cellular and tissue-based products. The agency is proposing to define "establish and maintain" in § 1271.3(ll) as "define, document (in writing or electronically), and implement, then follow, review, and as needed, revise on an ongoing basis." FDA intends, by using the phrase "establish and maintain" in these regulations, to indicate that, once established, procedures must be followed on an ongoing basis. Because established procedures would, by definition, be documented in writing or electronically, the agency is proposing to use the term "procedures" as opposed to "written procedures."

Procedures required under proposed § 1271.180, and those specifically required elsewhere in subpart D of part 1271, would be required to be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable diseases through the use of human cellular and tissue-based products by ensuring that: (1) The products do not contain relevant communicable disease agents; (2) the products do not become contaminated during manufacturing; and (3) the function and integrity of the products are not impaired through improper manufacturing. Procedures must be designed to ensure compliance with the requirements of part 1271.

The recovery of cells or tissue is an example of an especially significant step in the manufacture of a human cellular or tissue-based product, for which procedures would have to be established. Under the terms of proposed § 1271.180, such procedures would need to include the use of procurement techniques designed to prevent the transmission of communicable disease agents and diseases by the product. In addition, procedures for recovery would have to be designed to ensure that the function and integrity of the procured cells or tissue are maintained during and after procurement.

All procedures shall be reviewed and approved by a responsible person prior to implementation. At least once in a 12-month period, all procedures would be required to be reviewed and, if necessary, revised; such review would need to be documented. Procedures must be readily available to personnel in the area where relevant operations are performed, unless this would be impractical. Any deviation from a procedure must be authorized by a responsible person, recorded, and justified.

FDA is not prescribing the contents of particular procedures, but is allowing establishments to develop procedures that suit their particular operations. Alternatively, under proposed § 1271.180, an establishment could adopt current standard procedures, e.g., those in a technical manual prepared by another organization, so long as the procedures are consistent with the requirements of part 1271, at least as stringent as those requirements, and appropriate for the establishment's operations.

Any procedure that becomes obsolete would be required to be archived for at least 10 years. Since some tissues have long expiration dates, they can be transplanted many years after they were recovered or processed. Should an adverse reaction occur after transplantation, it would be important to know the procedures under which the tissue was recovered or processed, especially if those procedures differ from the ones currently in place.

F. Facilities, Environmental Control and Monitoring, Equipment, and Supplies and Reagents

1. Facilities (Proposed § 1271.190)

Under proposed § 1271.190, any facility used in the manufacture of human cellular or tissue-based products must be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations. A facility that, for whatever reason, cannot be adequately cleaned is not appropriate for use in the manufacture of human cellular and tissue-based products, because of the potential risk of product contamination. "Relevant maintenance" refers to those actions that, if not taken, could lead to potentially adverse effects on product integrity or function, or to the accidental exposure of human cellular and tissue-based products to communicable disease agents, or to contamination or cross-contamination with such agents. Finally, any operation undertaken by a manufacturing establishment needs to be performed in a facility in which the operation can be performed correctly. For example, although not specifically required to do so by these regulations, an establishment may need to establish gowning procedures for its employees, in order that their functions be performed properly. Such an establishment would need to provide employees with a dressing room and gowning area.

Proposed § 1271.190 would also require that a facility be maintained in a good state of repair. Broken windows, peeling paint, uneven flooring, and improper electrical wiring are all examples of maintenance problems that could lead to product contamination or impairment of product function or integrity. In addition, adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities would all be required.

Proposed § 1271.190(b) sets out requirements for the location of operations within a facility used in the manufacture of human cellular or tissue-based products. Such a facility would need to be divided into separate or defined areas of adequate size for each operation that takes place in the facility. As an alternative, however, other control systems could be established and maintained to prevent improper labeling, mix-ups, contamination, cross-contamination,

and accidental exposure of human cellular and tissue-based products to communicable disease agents. Examples of different types of operations that an establishment might perform, and which would need to be conducted either in separate locations or subject to other controls, include: (1) Receipt, identification, and storage of containers, labels, supplies, and reagents; (2) processing, including laboratory functions; (3) storage of human cellular and tissue-based products, both before and after release from quarantine; (4) product labeling; (5) storage and disposal of biohazards and/or medical waste; (6) irradiation; and (7) sterilization and aseptic processing.

Proposed § 1271.190(c) contains basic requirements for facility cleaning and sanitation. Facilities must be maintained in a clean, sanitary, and orderly manner. Sewage, trash, and other refuse must be disposed of in a timely, safe, and sanitary manner. Procedures for facility cleaning and sanitation would be required to be established and maintained. These procedures would need to include an assignment of responsibility for sanitation, cleaning methods to be used, and a cleaning schedule. Finally, all significant cleaning and sanitation activities that are done to prevent contamination would need to be documented, and records maintained.

2. Environmental Control and Monitoring (Proposed § 1271.195)

Proposed § 1271.195 would require monitoring and control over environmental conditions where such conditions (e.g., temperature, air quality) could reasonably be expected to have an adverse effect on the function or integrity of human cellular and tissue-based products, to cause contamination or cross-contamination of products or equipment, or to lead to accidental exposure of products to communicable disease agents. In these situations, an establishment would be required to establish and maintain procedures to adequately control and monitor environmental conditions and to provide proper conditions for operations.

Depending on the particular environmental factors at a facility, and the type of operations that take place there, environmental controls and monitoring could include one or more of the following: Temperature and humidity controls; ventilation and air filtration; cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; maintenance of equipment used to control conditions necessary for aseptic processing operations; and environmental monitoring for organisms. Proposed § 1271.195(a) would require these elements to be adopted, where appropriate. Thus, under proposed § 1271.195, an establishment would be required first to identify any environmental conditions that require monitoring and control, and then to respond appropriately.

Periodic inspections of environmental controls systems would be required. In addition, environmental controls and monitoring activities would have to be documented, and records maintained.

3. Equipment (Proposed § 1271.200)

CGTP requirements for equipment are set out in proposed § 1271.200. For human cellular and tissue-based products to be manufactured properly, the equipment used in their manufacture must be appropriate. Thus, § 1271.200(a) contains the general requirement that equipment used in the manufacture of human cellular and tissue-based product be of appropriate design for its use. Equipment must be suitably located and installed to facilitate operations, including cleaning and maintenance. In addition, equipment must not have any adverse effect on the products being manufactured.

Equipment used for inspection, measuring, and testing must be capable of producing valid results; such equipment could include automated, mechanical, electronic, computer, or other kinds of equipment. Section 1271.200(c) would require regularly scheduled calibration of equipment used for inspection, measuring, and testing. Thus, for example, a thermometer used in a storage area would be required to produce valid results and would also be subject to regularly scheduled calibration procedures. "Equipment used for inspection" would include any equipment used to inspect a human cellular or tissue-based product during its manufacture or prior to making it available for distribution.

Under § 1271.200(b), an establishment would be required to establish and maintain procedures for cleaning, sanitizing, and maintaining equipment. The purpose of these procedures is to prevent equipment malfunctions, contamination or cross-contamination, accidental exposure of human cellular and tissue-based products to communicable disease agents, and other events that could reasonably be expected to have an adverse effect on product function or integrity. Cleaning, sanitizing, and maintenance of equipment would be required to be performed according to established schedules.

Section 1271.200(d) sets out a requirement for routine inspections of equipment for cleanliness, sanitation, and calibration, and to ensure compliance with maintenance schedules.

Section 1271.200(e) contains specific requirements for records, to be maintained in accordance with the general records provisions in § 1271.270. All maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with § 1271.200 would be required to be documented. Records of recent maintenance, cleaning, sanitizing, calibration, and other activities must be available at each piece of equipment; this requirement promotes both accurate recordkeeping and ease of reference. In addition, the use of each piece of equipment must be documented, and this record of use must identify each human cellular or tissue-based product manufactured using the equipment. This requirement is necessary to ensure that those products manufactured with a particular piece of equipment may be traced for follow-up and appropriate corrective action, in the event that a problem (e.g., contamination or malfunction) is discovered after the equipment is used.

4. Supplies and Reagents (Proposed § 1271.210)

Use of a contaminated or otherwise defective supply or reagent in the manufacture of a human cellular or tissue-based product could adversely affect the product; e.g., by introducing a disease agent or by failing to properly preserve the product. For this reason, compliance with CGTP requires that care be taken in receiving supplies and reagents into an establishment, in determining their appropriateness for use, and in keeping track of the products in whose manufacture they are used. By "supplies and reagents," the agency refers to all of the products that might be used during the manufacturing process but excludes any material that might be considered to become a component of a human cellular or tissue-based product. Supplies and reagents would include, but not be limited to, "processing material," which the agency is proposing to define at § 1271.3(hh) as "any material or substance that is used in, or to facilitate, processing, but which is not intended by the manufacturer to be included in the human cellular or tissue-based product when it is made available for distribution."

Proposed § 1271.210 contains several requirements with respect to supplies and reagents used in the manufacture of human cellular and tissue-based products. An establishment would be required to establish and maintain procedures for receiving supplies and reagents. Before using a supply or reagent, the establishment must verify that the supply or reagent meets specifications that are designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through product contamination or the impairment of product function or integrity. An establishment could verify on its own that the supplies and reagents that it uses meet specifications; e.g., by testing the product. Alternatively, verification could be accomplished by the vendor of the supply or reagent. "Verification" is defined in proposed § 1271.3(ss) as "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."

Section 1271.210(b) would require that reagents used in processing and preservation of human cellular and tissue-based products be of appropriate grade for their intended use and, if appropriate, sterile. Some establishments may produce their own in-house reagents. These establishments would be required to validate and/or verify the procedures for producing such reagents.

Section 1271.210(c) would require that specific records relating to the receipt, verification, and use of each supply and reagent be maintained.

G. Processing

Three sections of the proposed CGTP regulations address the processing of human cellular and tissue-based products. Proposed § 1271.220 would require controls to be established over processing. Requirements for making changes to processes are contained in proposed § 1271.225. Proposed § 1271.230 would require process validation in place of verification in some situations and sets out certain specific requirements related to process validation.

"Processing" is defined in proposed § 1271.3(mm) as "any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution performed on a human cellular or tissue-based product, including, but not limited to, preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage."

1. Process Controls (Proposed § 1271.220)

Under proposed § 1271.220(a), any establishment engaged in the processing of human cellular and tissue-based products would be required to develop, conduct, control, and monitor its manufacturing processes to ensure that each product: (1) Conforms to its specifications, (2) is not contaminated, (3) maintains its function and integrity, and (4) is manufactured so as to prevent transmission of communicable disease by the product. By "specifications," the agency refers to those criteria established by a manufacturer for a human cellular or tissue-based product that must be met at defined stages in the manufacturing process and before the product is made available for distribution.

Sections 1271.220(b) governs the removal of processing materials. In accordance with the definition proposed in § 1271.3(hh), processing materials would not be intended by the manufacturer to be included in a human cellular or tissue-based product when it is made available for distribution. Under § 1271.220(b), where a processing material could reasonably be expected to have an adverse effect on a human cellular or tissue-based product's function or integrity, the establishment would be required to establish and maintain procedures for the use and removal of the processing material to ensure that it is removed or limited to an amount that does not adversely affect the product's function or integrity. Any such removal or reduction would be required to be documented.

Section 1271.220(c) would prohibit the pooling of human cells or tissue from two or more donors during manufacturing. Pooling refers to placing products in physical contact with each other or mixing them in a single receptacle. Such commingling of cells or tissues from a single infected donor with cells or tissues from other donors can contaminate the entire pooled quantity, greatly increasing the risk to recipients of the pooled materials of exposure to infectious agents. The proposed regulation is consistent with recommendations made by FDA's Transmissible Spongiform Encephalopathy Advisory Committee, at their meeting on October 6, 1997, with respect to the pooling of dura mater.

Section 1271.220(d) would require procedures to be established for in-process monitoring, or monitoring of the product during processing, for compliance with specified requirements. This requirement is modified by the phrase "where appropriate." In other words, as discussed in section II.A.4. of this document, in-process monitoring would be required unless the establishment can justify, and document, that it would be unnecessary under the terms of § 1271.150(d). The in-process product would have to be controlled until the completion of any required inspection, tests, or other verification activities, or until any necessary approvals are received and documented. Any sampling taken of the in-process product for the purpose of testing or inspection would be required to be representative of the material being evaluated.

2. Process Changes (Proposed § 1271.225)

Proposed § 1271.225 would require an establishment to establish procedures for making changes to a process. Any such change would have to be verified or validated, to ensure that the change does not create an adverse impact elsewhere in the operation. Any change would also have to be approved by a responsible person with appropriate knowledge and background before being implemented. Proposed § 1271.225(b) would require that records be kept of all such changes, and sets out the required elements of such records (e.g., the rationale for the change).

3. Process Validation (Proposed § 1271.230)

Proposed § 1271.230 contains requirements related to the validation of processes. Process validation, under proposed § 1271.3(rr), means "establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications."

Proposed § 1271.230(a) would require establishments to validate their processes where verification is not feasible; e.g., where verification cannot be performed on each and every finished product. Thus, § 1271.230(a) states that, where the results of a process cannot be fully verified by subsequent inspection and tests, the process must be validated and approved according to established procedures, and the validation activities must be documented.

Under § 1271.230(b), any claim made in labeling or promotional materials that is related to the process used to manufacture a human cellular or tissue-based product must be based on a process that has been validated. Validation must be documented, and evidence of the validation must be maintained at the establishment and made available for review on inspection. Examples of such process-related claims

include the claim that a product is sterile or that it has undergone viral inactivation.

The agency is proposing in § 1271.230(c) a requirement that would apply specifically to establishments that process dura mater. Donor screening and testing requirements for donors of dura mater have been proposed in the donor-suitability proposed rule, but additional processing safeguards are necessary to prevent the transmission of Creutzfeldt-Jakob disease (CJD) (64 FR 52696 at 52706). Proposed § 1271.230(c) would require that dura mater be processed using a validated procedure to reduce CJD infectivity, while preserving the clinical utility of the product. Currently, an example of such a procedure would be a sodium hydroxide (NaOH) protocol that has been validated to reduce CJD infectivity (in an animal model) while preserving the tissue's clinical utility. In the future, other methods that more effectively reduce CJD infectivity may be developed.

If processes are validated, in place of verification, then procedures must be established and maintained to ensure that the specified requirements continue to be met; this requirement appears in proposed § 1271.230(d). Under § 1271.230(e), any change or deviation from a validated process would require a review and evaluation of the process and, where appropriate, revalidation.

H. Labeling Controls (Proposed § 1271.250)

Under proposed § 1271.250, an establishment would be required to establish and maintain procedures to control the labeling of human cellular and tissue-based products. These control procedures would be designed to ensure that products are identified properly and to prevent mix-ups. The agency is not specifying how such controls should be designed, but notes that they would likely need to include such elements as proper storage methods to prevent deterioration of adhesives, among other problems. In addition, § 1271.250 would require procedures to include verification of label accuracy, legibility, and integrity. Thus, for example, a labeled product would be checked under such verification procedures to ensure that its label was affixed securely to the container, could be read with ease, and accurately identified the product by identifier and product type.

Proposed § 1271.250 would also require that procedures be established and maintained to ensure that products are labeled in accordance with all applicable labeling requirements. "Applicable labeling requirements" for human cellular and tissue-based products regulated as biological drugs include the labeling regulations in parts 201 and 610 (21 CFR parts 201 and 610); for products regulated as devices, they include those in part 801 (21 CFR part 801). Other labeling requirements appear in several sections of proposed part 1271, and these are listed in proposed § 1271.250. For example, § 1271.90 is cross-referenced in § 1271.250; it would require that banked cells and tissues for autologous use be labeled "FOR AUTOLOGOUS USE ONLY" (donor-suitability proposed rule (64 FR 52723)). Procedures established in compliance with proposed § 1271.250 would need to ensure that banked cells and tissues for autologous use were labeled with this statement.

I. Storage (Proposed § 1271.260)

Proposed § 1271.260 sets out storage requirements. The proposed regulation addresses three general areas of concern: Control of storage areas; storage temperature; and expiration date.

Under proposed § 1271.260, each establishment would be required to establish and maintain procedures for the control of storage areas and stock rooms in order to prevent mix-ups, commingling, deterioration, contamination, and cross-contamination of human cellular and tissue-based products and supplies, as well as any other condition that might adversely affect product function or integrity. In addition, controls would be required to prevent improper release for distribution.

Storage at a proper temperature, in order to preserve a product's function and integrity and prevent deterioration, is an important aspect of CGTP. FDA recognizes that appropriate temperatures may differ for various types of products. Thus, § 1271.260(b) would require an establishment to establish acceptable temperature limits for the storage of human cellular and tissue-based products at each step of the manufacturing process. Monitoring of storage temperatures would be required. Temperatures would have to be documented, and recorded temperatures reviewed periodically to assure that temperatures remained in the permissible range.

Different products may be stored for differing lengths of time before use. The maximum storage period depends on such factors as product type, processing procedures and method of preservation, storage conditions, and type of packaging. Section 1271.260(c) would require, where appropriate, that an expiration date be assigned for each human cellular or tissue-based product.

Under § 1271.260(d), corrective action must be taken and documented whenever proper storage conditions are not met.

J. Receipt and Distribution (Proposed § 1271.265)

Proposed § 1271.265 covers the receipt and distribution of human cellular and tissue-based products. Section 1271.265(a) contains general requirements for procedures and recordkeeping. Section 1271.265(b) governs receiving activities. Requirements that must be met prior to making a product available for distribution are contained in § 1271.265(c). The remaining paragraphs deal with packaging, shipping conditions, and the return of products to inventory.

Under § 1271.265(a), procedures would be required for receiving, accepting or rejecting, and distributing human cellular and tissue-based products, as well as for the destruction or other disposition of such products. Each of these activities, when performed, must be documented. Required documentation would include the identification of the human cellular or tissue-based product, the activities performed and the results of such activities, the date or dates of the activity, the quantity of product subject to the activity, and the disposition of the product. The disposition of the product would include, for example, the identity of the consignee. Complete and accurate identification of a consignee would include not only the consignee's name, but its address and telephone number.

Section 1271.265(b) contains specific requirements with respect to the receipt of human cellular and tissue-based products for processing, distribution, or any other step in the manufacturing process. As part of its receiving activities, an establishment would be required to inspect incoming human cellular and tissue-based products, according to established procedures, for damage, contamination, deterioration, or any other indication that the integrity of the product had been impaired. The establishment would then determine whether to accept or reject the product. Acceptance or rejection of the incoming product would need to be documented.

An establishment receiving a human cellular or tissue-based product would also be required to ascertain its status and handle the product appropriately. For example, a product that is shipped under quarantine, pending completion of the donor-suitability determination required under subpart C of part 1271,

would be required to be maintained in quarantine after its receipt until the determination was complete. Other issues of product status (e.g., stage in processing, results of donor screening and testing) would dictate other appropriate action with respect to the product.

Proposed § 1271.265(c) deals with an establishment's determination that a product is "available for distribution," a term that the agency is proposing to define in proposed § 1271.3(ff). Under that definition, a human cellular or tissue-based product is "available for distribution" if it has been determined to meet all release specifications and to be suitable for distribution. Under § 1271.265(c), an establishment would be required to establish and maintain procedures for making products available for distribution, including developing release criteria. These procedures would be designed to prevent the release of products that are in quarantine, have deteriorated, or otherwise have been manufactured in violation of CGTP. They must also prevent the release of products from donors who have not been determined to be suitable, except as provided under proposed §§ 1271.65 and 1271.90.

Prior to making a human cellular or tissue-based product available for distribution, an establishment would be required to review all records pertaining to the product and to verify and document that release criteria have been met. The determination that a product is available for distribution must be documented and dated by a responsible person.

Under § 1271.265(d), all packaging and shipping containers would be required to be designed, validated, and constructed so as to ensure product function and integrity and to protect the product from damage, deterioration, contamination, or other adverse effects during customary conditions of processing, storage, handling, and distribution. Section 1271.265(e) would require that appropriate shipping conditions, to be maintained during transit, be defined for each type of product. And § 1271.265(f) would require that an establishment develop procedures for determining whether a product that is returned to the establishment may be returned to inventory.

K. Records (Proposed § 1271.270)

Proposed § 1271.270 contains general requirements for recordkeeping under part 1271. Section 1271.270(a) would require establishments to maintain records concurrently with the performance of each significant step required in subparts C and D of part 1271. Many, but not necessarily all, of the requirements for documenting a manufacturing activity are specifically noted elsewhere in the regulations. For example, an establishment's receipt of tissue for processing would be a significant step that needs to be documented; proposed § 1271.265(a) lists the specific documentation that would be required. As noted in proposed § 1271.270(a), any requirement in part 1271 that an activity be documented involves the creation of a record, and that record would be subject to the requirements of § 1271.270.

Section 1271.270(a) would require records to be accurate, indelible, and legible. Entries must be dated and the person performing the work in question must be identified. Records would have to be sufficiently detailed to provide a complete history of the work performed and to relate the records to the particular human cellular or tissue-based product involved. In order to protect the privacy of both donors and recipients, adequate record security systems would be required.

Under § 1271.270(b), establishments would have the flexibility to develop individualized systems of maintaining and organizing their records, so long as certain objectives were achieved. Records could be maintained in more than one location, provided that the records management system was designed to ensure prompt identification, location, and retrieval of all records. Further, the records management system would need to facilitate the review of a particular human cellular or tissue-based product's history both prior to its release for distribution and, if necessary, at a later date as part of a follow-up evaluation or investigation. In addition to records pertaining to individual products, records for product types would be required to be maintained and organized. Thus, for example, a manufacturer of several different types of human cellular and tissue-based products would be required to maintain, for each product type, records of pertinent procedures, product specifications, labeling and packaging procedures, and equipment logs. A records management system could be as simple as keeping all information pertaining to the manufacture of one product in one file folder, and keeping all file folders for one product type, e.g., tendons, in one drawer of the file cabinet. This drawer, labeled "Tendons", would also contain a folder for "generic" procedures common to all tendons. A more elaborate records management system could utilize a computer to generate files and subfiles.

Section 1271.270(d) and (e) deal with methods and time frames for retaining records. Under § 1271.270(d), records could be maintained electronically, as original paper records, or as true copies. Examples of true copies include photocopies, microfiche, and microfilm. Suitable equipment would be required to be available for reading and photocopying any records maintained on microfiche or microfilm. Records stored in automated data processing systems must be backed up to prevent their loss. Any electronic record or electronic signature would be subject to the requirements in 21 CFR part 11.

Under § 1271.270(e), all records would be required to be kept for 10 years after their creation. However, consistent with proposed § 1271.55(b) on records of donor-suitability determinations, records pertaining to a particular human cellular or tissue-based product must be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product. See donor-suitability proposed rule (64 FR 52721). If the date of implantation, transplantation, infusion, or transfer is not known, then the records must be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. The establishment must make provisions for all records to be maintained for the required period in the event that the establishment ceases operation. FDA requests comment on whether there are specific types of records for which a retention period shorter than 10 years would be appropriate and would not compromise the agency's ability to prevent the introduction, transmission and spread of communicable disease.

Section 1271.270(c) cross-references records requirements proposed in subpart C of part 1271 that relate to donor testing and screening, in order to make clear that records required under subpart C of part 1271 are subject to the recordkeeping requirements in § 1271.270. Section 1271.270(f) would require an establishment to maintain records of contracts, agreements, and other arrangements with other establishments under which any step in the manufacturing process is performed by the other establishment. These records would need to contain not only the name and address of the other establishment, but also a description of each party's responsibilities.

L. Tracking (Proposed § 1271.290)

FDA considers product tracking to be an essential component of its proposed

regulatory system for human cellular and tissue-based products. Should the recipient of such a product contract a communicable disease, tracking would permit appropriate follow-up, such as an investigation to determine whether the human cellular or tissue-based product transmitted the disease agent and, if so, would permit steps to be taken to prevent the distribution of other similarly infected products. Similarly, if a donor is discovered, post-donation, to have had a communicable disease, tracking would permit an establishment to locate products from that donor. Thus, a tracking system is closely linked to the agency's regulatory objective of preventing the spread of communicable disease.

As with other components of these CGTP regulations, FDA is proposing certain basic requirements, but is allowing establishments flexibility in designing tracking programs that suit their particular activities. Auditing of an establishment's tracking method to ensure its effectiveness would be required under the quality program (proposed § 1271.160(b)(8) and (d)). FDA recognizes that some establishments have already developed and implemented tracking systems and requests comments from those establishments on the success or failure of particular tracking methods.

Part 821 (21 CFR part 821) of FDA's regulations contains the medical device tracking requirements. Except for dura mater, human cellular and tissue-based products regulated as devices generally have not been subject to tracking under part 821; thus, there will be little or no duplication of tracking requirements. When a human cellular or tissue-based product is designated as a "tracked device," and subject to the device tracking regulations, the manufacturer would be required to satisfy both sets of tracking requirements. However, given the variety of methods that could be devised to satisfy the tracking requirements proposed in § 1271.290, it is foreseeable that a single tracking method could be adopted that conforms with the requirements of both § 1271.290 and part 821.

Proposed § 1271.290 would require each human cellular or tissue-based product to be tracked. Section 1271.290(a) would place the tracking obligation on each establishment that performs any step in the manufacture of a human cellular or tissue-based product.

Proposed § 1271.290(b) would require the establishment to establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from the donor to the recipient or final disposition and conversely from the recipient or final disposition to the donor. FDA recognizes, however, that some establishments may be better equipped than others to establish an effective tracking system. For this reason, the agency proposes to permit an establishment that performs some, but not all, of the steps in the manufacturing process to participate in a method of product tracking that has been established by another establishment responsible for other steps in the manufacturing process, provided that the tracking method meets all the requirements of § 1271.290. One possible method of tracking would be to collect information about recipients on cards that are returned to the tracking establishment.

Section 1271.290(c) would require that each human cellular or tissue-based product be assigned and labeled with a distinct identification code (e.g., alphanumeric) that relates the product to the donor and to all records pertaining to the product. Except in the case of autologous or directed donations, such a code must be created specifically for tracking and may not include an individual's name, social security or medical record number. An establishment that receives a human cellular or tissue-based product for further manufacturing might use the code already assigned or might assign a new identifier to the product. The regulation specifies, however, that an establishment that assigns a new identifier to a product shall establish and maintain procedures for relating the new identifier to the old identifier.

Section 1271.290(d) would require establishments to ensure, through agreements with consignees or through other measures, that the code and type of each human cellular or tissue-base product that is implanted, transplanted, infused, or transferred into a recipient be recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor. Section 1271.290(e) would require an establishment to document and maintain records of the disposition of each of its human cellular or tissue-based products to enable tracking from the donor to the recipient or final disposition. The information to be maintained must permit the prompt identification of the recipient of the product.

Under § 1271.290(f), an establishment would be required to inform its consignees in writing of the requirements in § 1271.290 and of the tracking method that the establishment is using to comply with those requirements. For example, a statement might be included in the materials accompanying the consigned human cellular or tissue-based product that would describe applicable regulations and the establishment's tracking method. The establishment would be required to document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of § 1271.290; this agreement would need to be obtained and documented upon initial distribution of human cellular or tissue-based products to a consignee and would not need to be obtained for each subsequent consignment.

Proposed § 1271.290(g) contains a requirement specific to donors of dura mater, intended to address the particular communicable-disease concerns associated with that type of product. Appropriate specimens from the dura mater donor would be required to be archived, under appropriate storage conditions, and for the appropriate duration, to enable future testing of the archived material for evidence of transmissible spongiform encephalopathy (TSE) and appropriate disposition of any affected dura mater tissue, if necessary. Although archiving samples may not immediately increase the assurance of safety for a dura mater graft, it would permit later testing for TSE-induced changes using improved or new methods as they become available. In the event that a dura graft recipient became ill with CJD, such testing of archival donor material would be needed to confirm whether the dura graft was the source of infection, so that no additional grafts from the affected lot would be distributed. At this time, based on currently available information, FDA recommends that samples of donor brain and dura mater tissues be archived at a temperature equal to or less than minus 70 ½C for 16 years beyond the product's expiration date.

Ideally, archived samples should be retained for the lifetime of the graft recipient, because the maximum incubation period is not certain. To date, the longest known incubation period is 16 years (Ref. 1). FDA believes that it may be unrealistic to expect a manufacturer to maintain an archive for such a long time. FDA suggests that establishment of a nationally supported archive be considered for prolonged storage of these materials, in order to further the study of iatrogenic transmission of spongiform encephalopathies.

M. Complaint Files (Proposed § 1271.320)

Proposed § 1271.320 would require establishments to maintain records of, and review, all complaints. "Complaint" is defined in proposed § 1271.3(ii) as:

any written, oral, or electronic communication that alleges: (1) that a human cellular or tissue-based product has transmitted or may have transmitted a communicable disease to the recipient of the product; (2) that the function or integrity of a human cellular or tissue-based product may have been impaired; or (3) any other problem with a human cellular or tissue-based product that could result from the failure to comply with current good tissue practice.

A communication from a physician expressing concern about possible product contamination would be a "complaint."

The proposed regulation would require establishments to establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints. Records of each complaint that the establishment receives would be required to be maintained in a file designated for complaints. The complaint file would be required to contain sufficient information about each complaint for proper review and evaluation of the complaint, including the identifier of the human cellular or tissue-based product that is the subject of the complaint. For example, the complaint file should include the date of each report, the unique product identifier, and the name of the person or establishment that submitted the complaint. Proposed § 1271.320 would require that the complaint file be made available for review and copying upon request from an authorized employee of FDA. Section 1271.320(c) sets out requirements for the review and evaluation of complaints.

III. Additional Requirements With Respect to 361 Products

Proposed subpart E of part 1271 contains reporting and labeling requirements that would apply only to those establishments that manufacture human cellular and tissue-based products as described in proposed § 1271.10 (registration proposed rule (63 FR 26754)). Such products would be products that: (1) Are minimally manipulated, (2) are not promoted or labeled for any use other than a homologous use, (3) are not combined with or modified by the addition of any nontissue or noncellular component that is a drug or a device, and (4) do not have a systemic effect. The agency proposes to regulate such products solely under the authority of section 361 of the PHS Act and not as biological drugs or devices. Thus the heading of subpart E of part 1271 is "Additional Requirements for Establishments Described in § 1271.10." Human cellular and tissue-based products regulated as biological drugs or as medical devices will continue to be subject to reporting and labeling requirements that are currently in place.

Although the title of proposed subpart E of part 1271 refers to "additional" requirements for establishments described in § 1271.10, the proposed reporting and labeling requirements are designed to be less extensive and burdensome than the current requirements applicable to products regulated as biological drugs or as devices. This approach is in keeping with the agency's expressed plans to put in place a tiered regulatory scheme, under which human cellular and tissue-based products would be subject to an appropriate level of regulation based on the degree of risk. At the same time, the proposed reporting and labeling requirements for 361 products have been drafted to be generally consistent with existing biological drug and device regulations.

A. Reporting Requirements (Proposed § 1271.350)

In order to stay informed of potential problems with human cellular and tissue-based products related to communicable-disease transmission, and to be able to take appropriate steps in response, FDA needs to receive information from establishments on adverse reactions and certain product deviations that could result in adverse reactions. For this reason, FDA is proposing to require two different kinds of reports from establishments that manufacture human cellular and tissue-based products regulated solely under section 361 of the PHS Act: the reporting of adverse reactions, and the reporting of product deviations.

1. Adverse Reactions

Under proposed § 1271.350(a), establishments would be required to report adverse reactions to CBER. The agency is engaged in an ongoing effort to enhance agency-wide consistency in the collection of safety data and, where possible, consistency with the definitions, reporting periods, formats, and standards recommended by the International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals for Human Use (ICH). See "Expedited Safety Reporting Requirements for Human Drug and Biological Products," final rule (62 FR 52237, October 7, 1997). In order to achieve a degree of uniformity throughout the agency and to simplify reporting requirements for firms, FDA has modeled the procedures in § 1271.350(a) on the reporting requirements for other regulated products (i.e., drugs, devices, and biological products) and is proposing to require use of the same standard reporting form that is already in use (FDA Form-3500A).

Proposed § 1271.3(gg) would define an adverse reaction as "a noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out)." This definition reflects the agency's intention to shift from adverse experience reporting to adverse reaction reporting, consistent with ICH guidelines (62 FR 52237 at 52238), and is consistent with the ICH E2A guideline's definitions of "adverse drug reaction," International Conference on Harmonisation; Guideline on Clinical Safety Data Management; Definitions and Standards for Expedited Reporting, availability (60 FR 11284 at 11285, March 1, 1995). Under the proposed definition, not all unsuccessful outcomes would be considered "adverse reactions." For example, the agency recognizes that a recipient may reject a human cellular or tissue-based product, or that there may be a failure to engraft (e.g., of hematopoietic stem cells), for reasons that are unrelated to the product itself. Or a procedure may fail for reasons that, whether or not specifically identified, are known not to be product-related. On the other hand, if the relationship between the product and the noxious and unintended response cannot be ruled out, the response would be considered an adverse reaction under the proposed definition.

The phrase "the relationship cannot be ruled out" is included in the proposed definition to clarify which individual cases should be reported to FDA. Instances of probable, possible, remote, or unlikely relationships would all be considered adverse reactions, because there would be at least a reasonable possibility that the noxious and unintended response may have been caused by the human cellular or tissue-based product, even though causality has not been established.

Under proposed § 1271.350(a), only those adverse reactions that involved the transmission of a communicable

disease, product contamination, or the failure of a human cellular or tissue-based product's function or integrity would be required to be reported. Moreover, reporting would be limited to those adverse reactions that are fatal or life-threatening, that result in permanent impairment of a body function or permanent damage to body structure, or that necessitate medical or surgical intervention.

In order to determine which adverse reactions are required to be reported, each establishment would be required to review all adverse reaction reports. The source of the information is not relevant; all reports, regardless of source, would have to be considered.

The procedures proposed for reporting adverse reactions are modeled on those used for other products regulated by the agency. Reports to the agency would be required within 15 calendar days of initial receipt of the information, with a possible follow-up report. Reports would be submitted to CBER. The proposed regulation provides addresses and information on obtaining forms.

With respect to human cellular and tissue-based products regulated as biological drugs, the reporting requirements in 21 CFR 600.80 continue to apply. For those products regulated as devices, the medical device reporting requirements in 21 CFR part 803 apply. The agency notes that the transmission of a serious communicable disease would constitute an event that is required to be reported under current regulations.

2. Product Deviations

FDA is proposing to require, in § 1271.350(b), that those product deviations that could reasonably be expected to lead to a reportable adverse reaction be reported to CBER, along with information on corrective actions. A definition of the term "product deviation" is proposed in § 1271.3(kk) and has been discussed at section II.C of this document.

In the proposed approach document, FDA indicated that establishments would be required to maintain records of errors and accidents, a term that is incorporated in this proposal within the meaning of "product deviation" (see proposed § 1271.3(kk)), and to make them available for inspection, but that no reports to the agency would be required. The General Accounting Office, in its report on human tissue banks, criticized the agency for not requiring that such records be reported (Ref. 2).

The agency is now proposing to require the reporting of certain product deviations: those that are of the type that could reasonably be expected to lead to a reportable adverse reaction. In addition, required reporting would be limited to product deviations involving human cellular or tissue-based products that have been distributed. The agency considers that these limitations on the reporting obligation will lessen the burden on establishments and on the agency, making it possible for the agency to receive meaningful information and respond appropriately (e.g., by monitoring recalls and assisting in their implementation as necessary and appropriate).

Proposed § 1271.350(b) sets out the requirements for reporting product deviations that could give rise to an adverse reaction and provides the address to be used. Reports of such product deviations would be expected as soon as possible. Although no particular reporting form would be required, § 1271.350(b)(2) states that each report shall contain a description of the product deviation and information on all corrective actions that have been or will be taken in response to the product deviation, such as recalls.

B. Labeling and Claims

Proposed § 1271.370 contains requirements for product labeling and would govern promotional claims made for human cellular and tissue-based products regulated solely under the authority of section 361 of the PHS Act. Section 1271.370(a) describes the required contents of product labels and accompanying materials. The types of claims that may be made for human cellular and tissue-based products are addressed in § 1271.370(b).

The agency considers regulation of labeling and promotion to be an essential part of its proposed tiered, risk-based regulatory system for human cellular and tissue-based products.

Labeling and promotional materials which contain incomplete, unclear, inaccurate, unbalanced, or misleading information can increase the risk of the introduction, transmission, or spread of communicable disease by misleading the public into inappropriate or unsafe practices regarding these products (e.g., storing a product at an incorrect temperature) or by hindering corrective action which might become necessary (e.g., by delaying identification of the establishment distributing an unsafe product).

For these reasons, the agency considers that section 361 of the PHS Act provides the agency with sufficient authority to issue these requirements.

1. Labeling Information

Proposed § 1271.370(a) would require each human cellular or tissue-based product made available for distribution to be labeled clearly and accurately. In addition, certain basic information would be required to appear on the product label: (1) The name and address of the establishment that determined that the product met release criteria and made the product available for distribution, (2) a description of the type of product, and (3) the product's expiration date, if any. The agency considers each of these items to be of sufficient importance that they warrant placement on the product label itself instead of in materials that accompany the product. The first two items are crucial for accurately identifying the product and responsible establishment in the event of any necessary follow-up action (e.g., adverse reaction reports). Requiring products to be labeled with their expiration dates helps to ensure that they maintain their function and integrity at the time of use.

Recognizing that space on the product label may be limited, the agency proposes to require that the following information appear either on the product label or in a package insert: (1) Storage temperature, (2) warnings, where appropriate, and (3) instructions for use. Information on storage temperature will help prevent errors in handling and help ensure that the product maintains its integrity and functions properly in the recipient. Warnings and instructions for use will inform the physician of the proper use of the product and would increase the probability of a successful procedure.

2. Claims

Section 1271.370(b) deals with claims for human cellular and tissue-based products in labeling, advertising, and promotional materials. Consistent with the agency's plans outlined in the proposed approach document, this provision would require that any such claim be clear, truthful, balanced, and not misleading. A "balanced" claim for a product would, for example, reflect an objective, unbiased view of the product, including not only claims for the product's benefits but also explanations of any hazards. A claim may be considered to be misleading if it omits important information.

Proposed § 1271.370(b)(2) is intended to clarify one of the four criteria that must be met for a human cellular or tissue-based product to be regulated solely under the authority of section 361 of the PHS Act. Under proposed § 1271.10, a 361 product is one that, in

addition to meeting other criteria, is not promoted or labeled for any use other than a homologous use (registration proposed rule (63 FR 26744 at 26754)). Section 1271.370(b)(2) explains that a labeling claim or promotional materials regarding the therapeutic or clinical outcome of a human cellular or tissue-based product (other than for reconstruction, replacement, repair, or supplementation of cells or tissue) would be considered a claim for a use other than a homologous use. A product for which such a claim was made would be subject, along with its labeling, to regulation under the act and/or section 351 of the PHS Act.

3. Labeling of Biological Drugs and Devices

Proposed § 1271.370 applies only to 361 products; human cellular and tissue-based products regulated as biological drugs or as devices will continue to be subject to labeling requirements currently in place. Parts 201 and 610 (21 CFR parts 201 and 610) will apply to human cellular or tissue-based products regulated as biological drugs, as will relevant statutory provisions and any conditions of product licensure. Human cellular and tissue-based products regulated as devices will be subject to the labeling requirements in part 801, in addition to the provisions of the act and any applicable conditions of approval or clearance.

In order to ensure that all human cellular and tissue-based products, regardless of regulatory category, bear certain basic relevant information, FDA proposes to interpret several current regulations as encompassing the information set out in proposed § 1271.370(a). The agency would expect the information listed in proposed § 1271.370(a) to appear on the label or package insert of those products regulated as biological drugs or devices.

The paragraphs below set out each item listed in proposed § 1271.370(a), along with the parallel regulation applicable to biological drugs or devices. The agency expects that few if any changes will need to be made to current labeling to ensure that the information listed in proposed § 1271.370(a) is provided. Where there is a difference in required placement of the information (e.g., on the label or in a package insert), the placement required in the biological drug or device regulation will apply.

a. *Name and address of the establishment that determines that the product meets release criteria and makes the product available for distribution.* For biological drugs, §§ 610.60(a)(2), 610.61(b), and 610.63 require the name, address, and license number of the manufacturer or, in the case of divided manufacturing responsibilities, all manufacturers. Section 610.64 permits the name of the distributor to appear. For human cellular and tissue-based products, FDA considers the establishment that determines that the product meets release criteria and makes the product available for distribution to be a manufacturer and will expect that manufacturer's name and address to appear on the product label.

Section 801.1(a) requires the label of a device to specify the name and place of business of the manufacturer, packer, or distributor. FDA proposes to interpret this requirement, with respect to human cellular and tissue-based products regulated as devices, as requiring the name of the establishment that determines that the product meets release criteria and makes the product available for distribution.

b. *Description of the type of product.* For biological drugs, §§ 610.60(a)(1) and 610.61(a) require the proper name of the product to appear on the container and package label. The product's proper name will serve as an adequate description of the type of product. For devices, section 502(e)(2) and (e)(4) of the act (21 U.S.C. 352(e)(2) and (e)(4)) requires products to be labeled with their established name, or if there is no established name, then with the common or usual name of the device; either will suffice, so long as it adequately describes the type of product.

c. *Expiration date.* For biological drugs, §§ 610.60(a)(4) and 610.61(d) require products to be labeled with their expiration dates. For devices, § 801.109(c) requires products to be labeled with information on "any relevant * * * precautions"; FDA proposes to interpret this provision as requiring a product's expiration date, if the product has one, because the expiration date is effectively a precaution against use of an out-of-date product.

d. *Storage temperature.* For biological drugs, § 610.61(h) requires the recommended storage temperature to appear on the package label. For devices, FDA proposes to interpret § 801.109(c), which requires information for use, including precautions, to include the proper storage temperature.

e. *Warnings, where appropriate.* For biological drugs, § 210.57(e) requires warnings. For devices, § 801.109(c) requires information on hazards, contraindications, side effects, and precautions, which FDA proposes to interpret as including any appropriate warnings.

f. *Instructions for use.* For biological drugs, § 610.61(i), (j), and (k), as well as § 201.57(c), requires instructions for use. For devices, instructions for use are required in § 801.109(b)(2) and (c).

IV. Inspection and Enforcement Provisions

Proposed subpart F of part 1271 contains provisions on inspections; human cellular and tissue-based products offered for import; and orders of retention, recall, destruction, and cessation of manufacturing. Subpart F of part 1271 would apply only to those establishments described in proposed § 1271.10; i.e., those establishments that manufacture human cellular and tissue-based products regulated under the authority of section 361 of the PHS Act and proposed part 1271, but not as biological drugs or as devices. Products that the agency is regulating as devices or biological drugs will be subject to the enforcement provisions of the act and applicable regulations.

The proposed inspection and enforcement provisions are based on those contained in part 1270, subpart D, which are currently applicable to human tissue intended for transplantation. These provisions were fully discussed in the rulemaking on part 1270 ("Human Tissue Intended for Transplantation," interim rule (58 FR 65514 and 65517 to 65518, December 14, 1993); "Human Tissue Intended for Transplantation," final rule (62 FR 40429 and 40439 to 40440, July 29, 1997).

Authority for the enforcement of section 361 of the PHS Act is provided for in part under section 368 of the PHS Act (42 U.S.C. 271). Under section 368(a) 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 (42 U.S.C. 271(a)). Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted (18 U.S.C. 3559, 3571(b)). Organizations may be fined up to $200,000 per violation not resulting in death and $500,000 per violation resulting in death (18 U.S.C. 3559, 3571(c)). In addition, Federal District Courts have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act.

A. Inspections (Proposed § 1271.400)

Proposed § 1271.400 addresses the inspectional process. In large part,

inspections of establishments that manufacture human cellular and tissue-based products would be conducted in the same manner as inspections of firms dealing in other FDA-regulated commodities.

Establishments subject to inspection include those that perform any step in the manufacture of human cellular and tissue-based products, including recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. All of these establishments, including any location performing contract services, would be required to permit inspections by an authorized FDA representative at any reasonable time and in a reasonable manner. The FDA representative would determine which areas of the establishment to inspect in order to determine compliance with the provisions of part 1271; these might include, but would not necessarily be limited to, the establishment's facilities, equipment, processes, products, procedures, labeling, and records.

Inspections would be made with or without prior notification and would ordinarily occur during regular business hours. The frequency of inspection would be at the agency's discretion.

The FDA representative would call upon the most responsible person available at the time of inspection of the establishment and could question the personnel of the establishment as the representative deems necessary. The FDA representative could review and copy any records required to be kept under part 1271, and could take photographs or make video tapes. The agency notes that, under the policy expressed in Compliance Policy Guide 7151.02, "FDA Access to Results of Quality Assurance Program Audits and Inspections," the FDA representative would not ordinarily review or copy an establishment's records and reports that result from audits of the establishment's quality program established under proposed § 1271.160, when such audits are conducted according to the establishment's written quality program. This policy is intended to encourage the establishment to conduct quality program audits that are candid and meaningful. The agency would continue to have access to all information required to be maintained under proposed part 1271, such as complaint files, information on product deviations, and information on corrective actions.

At the end of the inspection, if possible violations of the regulations are found, the FDA representative would issue to the most responsible person at the establishment a list of "Inspectional Observations" (Form FDA–483), describing the observations of the representative that represent an observed or potential problem with the facility or with the human cellular and tissue-based products. After the report of the FDA representative is reviewed, FDA may issue additional correspondence to the establishment describing the violations to the regulations and requesting appropriate follow-up action.

The public disclosure of records containing the name or other positive identification of donors or recipients of human cellular or tissue-based products would be handled in accordance with FDA's procedures on disclosure of information as set forth in 21 CFR part 20. Under these procedures, FDA takes necessary precautions to protect the privacy of names of donors and recipients prior to public disclosure of records containing identifiers of the donor and recipients. FDA recognizes the sensitive nature of information that would identify a human tissue donor or recipient. FDA may copy records containing identification of the donors or recipients if such records are needed; for example, to document the distribution of potentially infectious human cellular and tissue-based products.

The agency invites additional comments on possible alternative inspection and enforcement provisions that would leverage agency resources, be cost-effective, and achieve the public health goals of the proposed rule. The agency welcomes comments on the advantages and disadvantages of various types of programs, such as joint agency-third party inspectional programs and joint Federal-State inspectional and enforcement programs, as well as any other alternative approach that would help ensure compliance with the proposed rule.

B. Imports (Proposed § 1271.420)

Proposed § 1271.420, which is derived from § 1270.42, is intended to clarify the administrative steps for the importation of human cellular and tissue-based products into the United States. Human cellular and tissue-based products that have been recovered from sources outside the United States can enter the country, and products that have been recovered from sources in the United States and then sent outside the United States for processing can reenter the country, consistent with the provisions of part 1271. All imported human cellular and tissue-based products would be required to be accompanied by appropriate records identifying the donor and the status of donor testing and screening in accordance with the records requirements proposed in the donor-suitability proposed rule.

As with other imports, when a human cellular or tissue-based product is offered for entry, the importer of record must notify the director of the FDA district having jurisdiction over the port of entry through which the product is imported or offered for import. "Importer of record" is defined in proposed § 1271.3(tt). The human cellular or tissue-based product offered for import must be held intact, under conditions necessary to maintain product function and integrity, prevent contamination, and prevent transmission of communicable disease, until it is released by FDA.

Human cellular and tissue-based products that are offered for import and found to be in violation of part 1271 would be subject to recall and destruction in accordance with § 1271.440.

C. Orders of Retention, Recall, Destruction, and Cessation of Manufacturing (Proposed § 1271.440)

Proposed § 1271.440 describes the procedures for the retention, recall, and destruction of human cellular and tissue-based products and for the cessation of manufacturing operations, and is derived in large part from § 1270.43. Section 1271.440(a) states that, upon a finding that a human cellular or tissue-based product or an establishment is in violation of the regulations in this part (and thus poses a risk of spreading a communicable disease), the agency may issue an order that the product be recalled and/or destroyed, as appropriate, or that it be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or until the safety of the product is confirmed. Alternatively, the agency may take possession of and/or destroy the violative product.

Section 1271.440(c) describes in further detail the order of retention, recall, or destruction, and describes possible alternatives to destruction. Section 1271.440(e) provides an opportunity for a hearing under 21 CFR part 16 and states that, if such a hearing is requested, any possible destruction of human cellular and tissue-based products would be held in abeyance pending resolution of the hearing request.

Proposed § 1271.440(a)(3) contains a provision not found in § 1270.43: an "order to cease manufacturing until compliance with the regulations of this part has been achieved." This type of order would bar an establishment from continuing its manufacturing operations

until the agency has determined that compliance has been achieved. The order will specify the regulations at issue, and will ordinarily specify the particular operations covered by the order (e.g., distribution, labeling, etc.). Operations may not resume without prior authorization of FDA.

Authority for this new provision derives from section 361 of the PHS Act, which states that, "[f]or purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, * * * destruction * * *, and other measures, as in his judgment may be necessary." The agency considers these new measures to be a necessary component of its new comprehensive approach to cell and tissue regulation, which includes the proposed establishment registration and product listing and the proposed CGTP requirements.

The agency recognizes that an order to retain particular human cellular and tissue-based products suspected of being in violation of the regulations may be appropriate in some instances, and intends to continue to issue such orders as necessary. However, such a limited action against a product or products may be an inadequate enforcement tool in some instances; e.g., when an establishment fails to comply with CGTP. In that situation, it may be more appropriate to take action directly against the establishment, rather than against the products of the establishment.

For example, an order to cease operations would be appropriate in the case of an establishment that failed to establish and maintain proper procedures under proposed § 1271.260(a) for storage of human cellular and tissue-based products in such a way as to prevent their cross-contamination. Such a failure to comply with CGTP would cause potential serious communicable-disease risk from all of the establishment's products. An order to retain or destroy particular products would not prevent the establishment from continuing its faulty practices and could therefore be inadequate.

The agency expects that, typically, an order of cessation may be directed only at the distribution of human cellular or tissue-based products and would not affect the rest of an establishment's operations. However, in some cases, the order might cover a particular step in the manufacturing process. And in egregious cases involving serious CGTP deficiencies, the order might cover all of a firm's operations.

V. Proposed Revocation of Part 1270

Part 1270 contains regulations governing infectious disease testing, donor screening, recordkeeping, and enforcement for human tissue intended for transplantation. Products currently subject to the provisions in part 1270 would be considered human cellular and tissue-based products under the definition in § 1271.3(e) and would be regulated under proposed part 1271. The agency has previously announced its intention that proposed part 1271 would supersede the regulations in part 1270 (donor suitability proposed rule (64 FR 52696)). After the regulations in part 1271 go into effect, the regulations in part 1270 will be unnecessary, confusing, and duplicative. For these reasons, the agency now proposes to revoke part 1270.

VI. Proposed Effective Date

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

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Economic Impacts

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

The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. Many of the establishments within the tissue industry would be classified as small business entities, and a number of these facilities will incur new costs. Because of the limits of information to characterize the current quality management practices at many of these facilities, and thus the increased effort required to meet the standards of CGTP, the cost impact on small business entities is uncertain. The FDA has therefore prepared an Initial Regulatory Flexibility Analysis.

A. Estimated Cost Impact

With the proposed CGTP rule, the FDA is furthering completion of the set of proposals that represent a comprehensive new system of regulating human cellular and tissue-based products. Manufacturers of tissue products may need to make certain changes to their operations to comply with the rule, such as creating new procedures and providing additional documentation. The proposed rule affects several industries involved in the manufacture of human cellular and tissue-based products. These include: Eye banks, conventional tissue banks, hematopoietic stem cell facilities, and reproductive tissue facilities.

FDA estimates are based on available administrative data on the number of facilities within each industry sector and the number accredited by various industry associations. Where good statistical data are not available, FDA's cost impact estimates have incorporated the quantified judgments of individual experts identified through contacts with the industry associations. Because of the lack of comprehensive data to characterize patterns of current practice within each affected industry sector, and the importance of this data in development of an accurate assessment of cost impact, FDA requests detailed industry comment on the number of facilities involved in the manufacture of cellular and tissue products, and the net change in quality assurance efforts

needed for those facilities to comply with the proposed rule.

1. The Number and Type of Entities Affected

The economic impact of the proposed rule is organized around four subgroups: eye banks, conventional tissue banks, stem cell facilities, and reproductive tissue facilities. The number of facilities and the percent of facilities that follow current industry standards are summarized in table 1 of this document. In estimating net new costs for facilities, it is critical to account for facility adherence to current industry standards. In a number of tissue manufacturing sectors the industry standards for many manufacturing operations meet or exceed the specifications in the proposed rule. Facilities following those standards should experience very little impact in complying with FDA-proposed standards.

As presented in table 1 of this document, FDA estimates that there are 114 eye banks currently operating in the United States, although the EBAA believes that the number of banks is declining and may currently be closer to 100. According to EBAA, virtually all operating eye banks currently comply with the industry (EBAA) medical and procedural standards for quality control. For eye banks, the costs associated with following the proposed rule result from additional quality assurance steps and process documentation as specified under the CGTP.

FDA estimates that 110 tissue banks are involved in the manufacture of other conventional tissue, e.g., pericardium, dura mater, heart valves, skin allografts, bone allografts, fascia, tendon, and ligaments (hereafter referred to as "conventional tissue banks"). Industry sources report that approximately 75 to 80 percent of these facilities currently follow the standards for tissue banking established by the AATB. For these facilities, there will be some additional cost associated with review of the proposed FDA rule and with alignment of their current procedures to FDA's requirements. There may also be some additional recurring cost, where documentation and quality control required under the proposed rule extend beyond current practice. For the remaining 20 to 25 percent of facilities not following the industry standard, the cost of compliance would be somewhat higher. These facilities may need to establish more formal procedures and quality control steps, and may need to devote added staff hours to performing these procedures and processing controls.

Facilities that produce stem cell products from peripheral blood or from umbilical cord blood would also be affected by the proposed rule. FDA finds that available data to estimate the number of peripheral blood stem cell (PBSC) facilities and current practices are quite limited. The actual number of PBSC facilities may range from 200 to 400. Of the estimated total involved in peripheral blood stem cell production, approximately 150 are currently accredited by the AABB and an estimated 130 have applied for accreditation by the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT). Industry sources estimate that approximately 80 of these facilities are seeking dual AABB/FAHCT accreditation, indicating an unduplicated count of approximately 200 PBSC facilities assumed to be accredited by AABB and/or FAHCT. However, the manufacturing practices of non-accredited facilities are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of peripheral blood or bone marrow facilities may be as high as 400[1] (i.e., 200 more than the number estimated to be accredited by AABB or FAHCT), but the number of IBMTR/ABMTR-estimated facilities that actually process peripheral blood (as opposed to bone marrow) is uncertain.

In addition, the proposed rule would apply to facilities involved with reproductive tissue, primarily sperm banks and Assisted Reproduction Technology (ART) facilities. For purposes of this discussion, references to ART facilities include infertility clinics, and andrology and embryology laboratories. The American Society of Reproductive Medicine (ASRM) has a membership of approximately 330 ART facilities. The ASRM also has a 1996 list of approximately 110 sperm banks operating in the United States. Based on conversations with consultants, most commercial sperm banking and most ART facilities currently adhere to industry standards similar to those in the proposed rule. The 20 largest sperm banks are estimated to handle 95 percent of the total volume of product for the industry, and these facilities are believed to follow industry standards that are comparable to the CGTP. According to industry consultants, approximately one-third of the 20 largest sperm banks are accredited by the AATB, and the remaining two-thirds are licensed by State health agencies, including the California Department of Health and the New York Department of Health. Sperm banks are also regulated under the Clinical Laboratory Improvement Amendment (CLIA) of 1988.

Andrology laboratories at ART facilities are also subject to CLIA 1988. The Committee on Laboratory Accreditation (COLA) and the Joint Commission on Accreditation of Health Care Organization (JCAHO), also inspect embryo laboratories for accreditation. The requirements for accreditation by the College of American Pathologists (CAP), which also accredits ART facilities, closely resemble those in the proposed CGTP rule, with a few exceptions. Consultants estimate that as many as 80 percent of ART facilities may currently comply with the CAP requirements.

TABLE 1.—ESTIMATED NUMBER OF FACILITIES THAT FOLLOW INDUSTRY STANDARDS

Affected Industry	Relevant Industry Standards	Percent of Firms Following Industry Standards
Eye Tissue: 100–114 facilities	EBAA[1]	100% facilities estimated compliant
Conventional Tissue: (e.g., pericardium, dura mater, heart valves, skin allograft, bone allograft) 110 facilities	AATB[2]	75–80% facilities estimated compliant
Stem Cells Peripheral Blood (PB): 400 facilities [uncertain]	AABB or FAHCT[3]	85% accredited facilities estimated compliant
	FAHCT	
Cord Blood (CB): 25 facilities		100% CB facilities compliant

[1] Based on the National Inpatient Sample of hospital discharge data collected by the Agency for Health Care Policy Research (AHCPR) in the Health Care Utilization Project (HCUP), a total of 7,300 stem cell transplants were performed in 1994, the most recent year reported. With the number of stem cell facilities ranging from 400 to 200, this would translate to a range of 18 to 37 transplants per facility per year. Based on the implied volume of product per facility per year, a total of as many as 400 facilities would seem unlikely if the number of transplants in 1994 were representative of the current volume of demand for stem cell products.

TABLE 1.—ESTIMATED NUMBER OF FACILITIES THAT FOLLOW INDUSTRY STANDARDS—Continued

Affected Industry	Relevant Industry Standards	Percent of Firms Following Industry Standards
Reproductive Tissue Sperm Banks: 110 facilities	AATB; CAP[4] accreditation; State Licensed (e.g., NY,CA); CLIA[5]-certified	20% facilities estimated compliant (accounting for 95% of all production)

TABLE 1.—ESTIMATED NUMBER OF FACILITIES THAT FOLLOW INDUSTRY STANDARDS—Continued

Affected Industry	Relevant Industry Standards	Percent of Firms Following Industry Standards
Reproductive Tissue ART[6] Facilities: 330 facilities	CAP accreditation; State licensed (e.g., NY,CA); ASRM[7] guidelines	approximately 80% facilities estimated compliant

[1]Eye Bank Association of America
[2]American Association of Tissue Banks
[3]Foundation for the Accreditation of Hematopoietic Cell Therapy
[4]College of American Pathologists
[5]Clinical Laboratory Improvement Amendments of 1988
[6]Assisted Reproductive Technology
[7]American Society for Reproductive Medicine

2. Estimated Impact on Industry Facilities

In the sections that follow, the agency considers each of the provisions of the proposed rule its estimated impact on facilities in the identified sectors of the tissue industry. The impact analysis distinguishes expected cost impacts based on both facility size and estimated current adherence with industry standards. As defined by the U.S. Small Business Administration, a small facility has revenues less that $5.0 million.

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART[2] Facilities* (Small/Large)
1271.150	CURRENT GOOD TISSUE PRACTICE: GENERAL	--	--	--	--	--
1271.155	EXEMPTIONS AND ALTERNATIVES	--	--	--	--	--
1271.160	ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM					
(b)(2)	Functions—Procedures for sharing information	$349 (95%)	$698/ $2,004 (23%)	$0/ $698 (0%/ 80%)	$698 (5%)	$698/ $0 (5%/ 0%)
(b)(3)	Functions—Corrective actions	$414 (95%)	$828 (23%)	$0/ $828 (0%/ 80%)	$828 (5%)	$828/ $0 (5%/ 0%)
(b)(7)	Functions—Investigations	$2,022 (95%)	$2,022 (23%)	$0/ $2,022 (0%/ 80%)	$2,022 (5%)	$2,022 /$0 (5%/ 0%)
(d)(1)	Audits—Annual	$414 (95%)	$828/ $1,656 (23%)	$0/ $828 (0%/ 80%)	$828 (5%)	$828/ $1,656 (50%)
(d)(3)	Audits—Report	$138 (95%)	$276 /$552 (23%)	$207 (95%)	$207 (5%)	$207/ $414 (50%)
(e)	Computers—Validate customized software	$2,040 (10%)	$2,040 (10%)	$2,040 (10%)	$2,040 (5%)	$2,040 (5%)
(f)	Procedures—Quality program					
	—Facility with minor deficiencies	$449 (95%)	$449/ $1,159 (23%)	$449 (80%)	$449 (80%)	$449/ $1,159 (80%)
	—Facility with major deficiencies	$2,191 (5%)	$2,191/ $4,359 (5%)	$0/ $2191 (0%/ 5%)	$2,191 (5%)	$2,191/$4,359 (5%)
	—Cost for additional quality control work	$1,236 (95%)	$1,236 (23%)	$1,236 (80%)	$1,236 (80%)	$1,236 (80%)
1271.170	ORGANIZATION AND PERSONNEL					
(b)	Competent performance of functions—Sufficient personnel	--	$15,560 (23%)	$0/ $15,560 (0%/ 95%)	$15,560 (5%)	$15,560 (5%)
(c)	Training	--	$2,348/ $3,104 (23%)	$0/ $2,348 (0%/ 95%)	$2,348 (5%)	$2,348/ $0 (5%/ 0%))
(d)	Records—Personnel	--	--	--	--	--
1271.180	PROCEDURES—GENERAL REQUIREMENTS	$8,280 (5%)	$8,280 (23%)	$0/ $8,280 (0%/ 95%)	$8,280 (50%)	$8,280 (50%)
1271.190	FACILITIES					
(a)	General	--	--	--	$14,000 (5%)	$14,000/$28,000 (5%/ 5%)
(b)	Operation-Separation of Operations	--	--	$0/$14,000 (0%/ 95%)	14,000 (5%)	$14,000/$28,000 (5%/ 15%)
(b)	General-Separation	--	--			

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]—Continued

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART[2] Facilities* (Small/Large)
(c)(3)	Facility cleaning and sanitation—Procedures	$299 (5%)	$299/ $471 (23%)	$299 (95%)	$299 (5%)	$299/ $471 (5%)
(c)(4)	Facility cleaning and sanitation—Records	– –	– –	– –	– –	– –
1271.195	ENVIRONMENTAL CONTROL AND MONITORING					
(a)	General—Procedures for ventilation and air filtration	– –	$299/ $471 (23%)	$299 (95%)	$299 (80%)	$299/ $471 (80%)
(b)	Inspections—Environmental control systems	$1,000 (5%)	– –	$1,000 (50%/ 95%)	$1,000 (20%)	$1,000/$2,000 (20%)
(c)	Records—Environmental control and monitoring activities	$162 (95%)	$162/ $324 (23%)	$162 (95%)	$162 (80%)	$162/ $324 (80%)
1271.200	EQUIPMENT					
(b)	Procedures and schedules—Cleaning, sanitizing, and maintenance	– –	$1,254/ $2,638 (23%)	$0/ $1,254 (0%/ 95%)	$1,343 (90%)	$1,343/$2,261 (90%)
(c)	Calibration of equipment	– –	$1,254/ $2,638 (23%)	$1,254 (95%)	$1,343 (5%)	$1,343/ $2,261(50%)
(d)	Inspections—Routine	$204 (95%)	$408/ $816 (23%)	$204 (95%)	$204 (5%)	$204/ $408 (5%)
(e)	Records—Maintenance, cleaning, sanitizing, and calibrating activities					
	—Keeping records of cleaning and calibration activities	$162 (95%)	$324/ $648 (23%)	$162 (95%)	$162 (5%)	$162/ $324 (5%)
	—Keeping records of the use of each piece of equipment	$648 (95%)	$1,296/ $2,592 (23%)	$1,296 (95%)	$1,296 (100%)	$1,296/$2,592 (100%)
1271.210	SUPPLIES AND REAGENTS					
(a)	Receipt and verification—Procedures	$100 (95%)	$299/ $471 (23%)	$100/ $299 (95%/ 95%)	$299 (5%)	$299/ $471 (80%)
(b)	Reagents—Procedures in-house	– –	$299/ $471 (23%)	$299 (95%)		
(c)(1)	Records—Receipt of supply or reagent	$162 (95%)	$162 / $324 (23%)	$0 / $162 (0%/ 95%)	$162 (5%)	$162 / $324 (5%)
1271.220	PROCESS CONTROLS					
(b)	Processing material—Procedures for the use and removal of damaging processing materials	$299 (95%)	$299/ $471 (23%)	$299 (95%)	$299 (90%)	$299/ $471 (90%)
(d)	In-process monitoring—Procedures	$349 (95%)	$349/ $1,002 (23%)	$698 (95%)	$349 (5%)	$349/ $1,002 (5%)
1271.225	PROCESS CHANGES					
(a)	Procedures—Process changes	$698 (95%)	$698/ $2,004 (23%)	$0 /$698 (0%/ 95%)	$698 (5%)	$698/ $2,004 (90%)
(b)	Change records	$414 (95%)	$414/ $828 (95%)	$414 (95%)	$414 (90%)	$414/ $828 (90%)
1271.230	PROCESS VALIDATION					
(a)	General	$1,570 (95%)	$1,570 (95%)	$1,570 (95%)	– –	– –
(d)	Procedures	$1,396 (95%)	$698 / $2004 (95%)	$698/ $1,396 (95%/ 95%)		
(e)	Changes and deviations—Revalidation	$785 (95%)	$1,570 (95%)	$1,055 (95%)		
1271.250	LABELING CONTROLS—PROCEDURES	$349 (5%)	$349 / $1,002 (5%)	$349 (5%)	$349 (5%)	$349 / $1,002 (5%)
1271.260	STORAGE	– –	– –	– –	– –	– –
1271.265	RECEIPT AND DISTRIBUTION					
(a)(1)	General—Document identification of product	$816 (5%)	$1,632/ $3,264 (5%)	$1,632/ $3,264 (5%)	$1,632 (5%)	$1,632/ $3,264 (5%)

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]—Continued

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART*[2] *Facilities* (Small/Large)
(b)	Receiving activities—Procedures	– –	$349/ $1,002 (23%)	$698 (95%)	$698 (5%)	$698/ $2,004 (5%)
(c)	Availability for distribution—Procedures	– –	$349/ $1,002 (23%)	$349/ $698 (95%)	$698 (5%)	$698/ $2,004 (5%)
(d)	Packaging—Validation	$1,296 (95%)	$1,296 (95%)	$544 (95%)	$544 (100%)	$544 (100%)
(f)	Return to inventory—Procedures	– –	$299/ $471 (23%)	$0/$399 (0%/ 95%)	$299 (5%)	$299/$471 (100%)
1271.270	RECORDS					
(a)	General	$648 (95%)	$0/ $648 (0%/ 95%)	$648 (95%)	– –	– –
(b)	Records management systems	$2,760 (95%)	$0/ $2,760 (0%/ 95%)	$2,760 (95%)	$2,760 (5%)	$2,760/$5,520 (50%)
(e)	Length of retention	$18 (5%)	$18 (50%/ 95%)	$18 (95%)	$18 (5%)	$18/$36 (5%)
1271.290	TRACKING					
(b)(1)	Method of product tracking-General method	$698 (5%)	$0/ $349 (0%/ 95%)	$349 (95%)	$349 (80%)	$349/ $1,002 (80%)
(e)	Recipient information	$1,632 (5%)	$0/ $3,264 (0%/ 95%)	$3,264 (95%)	– –	– –
(f)	Consignees	$1,380 (5%)	$1,380 (23%)	$1,380 (95%)	$1,380 (80%)	$1,380 (80%)
1271.320	COMPLAINT FILE					
(a)	Procedures	$100 (95%)	$299/ $471 (23%)	$299 (95%)	$299 (5%)	$299/ $471 (5%)
(b)	Complaint file	– –	– –	– –	– –	– –
(c)	Review and evaluation of complaints	$552 (95%)	$552 / $1,104 (23%)	$552 (95%)	$552 (5%)	$552 / $1,104 (5%)
	E—ADDITIONAL REQUIREMENTS FOR ESTABLISHMENTS DESCRIBED IN 1271.10					
1271.350	REPORTING	– –	– –	– –	– –	– –
1271.370	LABELING AND CLAIMS	– –	– –	– –	– –	– –
	F—INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 1271.10					
1271.400 (a)	INSPECTIONS Inspections—General	$708 (100%)	$708 (100%)	$708 (100%)	$708 (100%)	$708 (100%)
1271.420	HUMAN CELLULAR AND TISSUE-BASED PRODUCTS OFFERED FOR IMPORT	– –	– –	– –	– –	– –
1271.440	ORDERS OF RETENTION, RECALL, DESTRUCTION, AND CESSATION OF MANUFACTURING	– –	– –	– –	– –	– –

[1]Only sections estimated to have compliance costs for these industries are shown. No cost is estimated for a section (indicated by a double dash"—") if the background analysis (see a detailed presentation of cost assumptions provided in FDA's *Cost Impacts of the Proposed Current Good Tissue Practices Rule on Eye Banks, Conventional Tissue Banks and Stem Cell Facilities: Background Paper*, April 1999, and in *Cost Impacts of the Proposed Current Good Tissue Practice Rule on Sperm Banks and ART Facilities*, February 1999, prepared by Eastern Research Group, Inc.) shows that the requirements: (1) Do not apply, (2) have no new cost impact, or (3) are met by another section of the proposed rule.
[2]Assisted Reproductive Technology

As indicated by the information in table 2, the impact of the proposed rule varies, depending upon the sector of the tissue industry and the particular provisions of the proposed rule. For many of the proposed provisions, the facility level impact will entail development of new procedures, or revision of existing procedures. The scope and degree of complexity may vary. FDA expects that the staff typically involved in the development and finalization of facility procedures will include technicians, clerical staff, lab supervisors, and the lab director. For purposes of industry-wide estimation, the agency's analysis relies on standardized estimates of the level of effort and cost for establishing procedures. Table 3 summarizes the agency's assumptions, based on input from industry consultants.[2]

[2]A detailed presentation of level of effort and cost assumptions are provided in FDA's "Cost Impacts of the Proposed Current Good Tissue Practices Rule on Eye Banks, Conventional Tissue Banks and Stem Cell Facilities: Background Paper," April 1999, and in "Cost Impacts of the Proposed Current Good Tissue Practice Rule on Sperm Banks and ART Facilities," February 1999, prepared by Eastern Research Group, Inc. These documents will be available on the CBER website.

TABLE 3.—ESTIMATED LEVEL OF EFFORT AND COST PER PROCEDURE REVISED OR PREPARED TO COMPLY WITH THE PROPOSED CURRENT GOOD TISSUE PRACTICE[1]

Size Category	Minor Procedures		Major Procedures	
Small Facility	Revise Existing	Prepare New	Revise Existing	Prepare New
Staff level of effort	2.0 hrs	6.0 hrs	8.0 hrs	16.0 hrs.
Cost	$99.50	$298.50	$349.0	$698.00
Large Facility				
Staff level of effort	4.0 hrs	12.0 hrs	27.0 hrs	54.0 hrs
Cost	$157.00	$471.00	$1,002.00	$2,004.00

[1]Small facilities are those with revenues less than $5.0 million. The distinction between major and minor procedures is described in the report by Eastern Research Group, Inc.

The analysis of impact is summarized below through a discussion of the proposed rule provisions and expected type and extent of industry impact. The pertinent section of the proposed rule is noted to facilitate reference to the related estimates in table 2.

a. *Section 1271.150—current good tissue practice: general.* The proposed rule would require manufacturers of human cellular and tissue-based products to follow CGTP. Section 1271.150(a) gives an overview of CGTP but does not present specific compliance requirements. The specific requirements are addressed in subsequent sections. Section 1271.150(b) would require that manufacturers ensure compliance on the part of contractors and proposes the establishment that should be responsible for compliance. FDA expects that facilities would use accredited referral laboratories to ensure compliance with the CGTP rule, and therefore new costs would be associated with § 1271.150(b). Section1271.150(c) explains the relationship of the proposed rule to regulations specifically applicable to biological drugs or devices and paragraph (d) defines the term "where appropriate" in relation to the rule. Neither § 1271.150(c) nor (d) would generate any costs for this industry because no compliance requirements are specified.

b. *Section 1271.155—exemptions and alternatives.* The proposed rule would allow establishments to request an exemption or alternative from FDA for any of the requirements of the rule. There is currently no basis for predicting industry requests for exemptions or alternatives, or for predicting the effect of these actions on compliance costs. FDA anticipates that very few facilities will consider it appropriate to be exempted from the quality standards specified in the proposed rule.

c. *Section 1271.160—establishment and maintenance of a quality program.* The proposed rule would require that facilities establish and maintain a quality program. The quality program would include: Procedures for each step in the manufacturing process, procedures for exchanging information with other establishments known to have recovered cells from the same donor, corrective action and documentation, training and education of personnel, appropriate monitoring systems, maintenance of records, investigation and documentation of all product deviations, other actions necessary to assure compliance with the quality program; assignment of authority over the quality control program, audits, computer software validation, and other procedures specific to the quality program. A number of these functions are further specified in subsequent provisions of the rule, and the impact is estimated in the context of those provisions.

In general, FDA anticipates that almost all of the establishments in the affected industries have the appropriate facilities, equipment, and systems to support comprehensive quality management, but only those already estimated to be following industry standards are expected to have comprehensive quality programs in place. Some facilities may need to upgrade their quality program for several of the proposed requirements. These include: Procedures for sharing information, corrective actions, and investigations. Further, some facilities may need to take additional steps to administer corrective actions and conduct investigations, if they currently do so only when major deviations arise.

Although sharing of information is an industry-wide practice, some small facilities, particularly those not following current industry standards, may not have written procedures and reporting forms for this task. FDA estimates that 95 percent of industry eye banks would need to revise a major procedure; 23 percent of other conventional tissue banks, not following the current AATB standard, would need to write a major procedure to comply with this requirement; 80 percent of the peripheral blood stem cell facilities not following the FAHCT or AABB standards would need to prepare a major procedure; and 5 percent of sperm banks and 5 percent of ART facilities would need to prepare a major procedure to address this requirement.

Although FDA anticipates that most industry facilities take steps to administer corrective actions and conduct investigations, some may currently do so only when major deviations arise.

FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, 80 percent of stem cell facilities, and 5 percent of sperm banks and ART facilities, would need to invest additional time. The incremental time for the laboratory director to administer corrective actions and document these activities is estimated to be an additional half-hour per month of laboratory director time at eye banks that already perform this activity to a lesser extent, and an additional hour per month at all other facilities that will be newly affected by this provision. As shown in table 2 in § 1271.160(b)(7) of the background papers prepared by FDA and Eastern Research Group Inc., (ERG) for newly required investigations in tissue facilities, FDA estimates an additional cost per year of $2,022 for an additional 2 hours per month for the laboratory director to investigate and document deviations, and an additional half hour each for the laboratory supervisor and technician to participate in the investigations.

A number of facilities would also institute other requirements of the quality program, including audits, computer software validation, and procedures specific to the quality program. Audits are part of the industry standards published by the AATB, the EBAA, by FAHCT and the AABB. However, some facilities following these standards may need to do some additional recordkeeping, and facilities not following standards would begin to conduct audits. Referring to table 2, FDA assumes that up to 95 percent of eye banks would increase their audit efforts, including additional lab director time to perform the audit and additional