hours of preparation for the annual audit. An estimated 23 percent of conventional tissue banks, and an estimated 50 percent of ART facilities, would allocate additional resources for annual audits, with a higher allocation of hours at larger facilities, to prepare for, and to conduct the audit. For stem cell facilities, FDA estimates that there would be no additional auditing required at facilities following FAHCT or AABB standards, but an estimated 80 percent of facilities not following industry standards would need to spend additional time to prepare for and to conduct an audit each year. It is also assumed that approximately 5 percent of sperm banks would allocate additional staff hours for these audit-related activities.

In addition to performing the annual audit, the proposed rule would require preparation of an annual audit report. Facilities following current industry standards may need to increase the time for reporting.

FDA estimates that 95 percent of industry eye banks will experience an increase of approximately 2 hours per year of lab director time for preparing the audit report. The 23 percent of conventional tissue facilities not following AATB standards are estimated to devote 4 hours of lab director time, in the case of small facilities, and 8 additional hours of lab director time at large facilities for the preparation of an annual audit report. Laboratory directors of 95 percent of the stem cell facilities, 5 percent of sperm banks, and 33 percent of ART facilities, would spend an estimated additional 3 hours to prepare the annual audit report. Approximately 17 percent of ART facilities would also be affected, with an increase of approximately 6 hours per year of staff time for audit report preparation.

Section 1271.160 of the proposed rule further stipulates that facilities would be required to validate the computer software used in their operations. The FDA assumes that off-the-shelf commercial software packages for particular applications are already validated by the software vendor, but that a facility's custom software would require complete software validation. FDA assumes that none of the affected facilities currently validate their custom software and that approximately 10 percent of eye, conventional tissue and stem cell facilities, and approximately 5 percent of reproductive tissue facilities have developed custom software that would require full software validation under the proposed rule. While the scope of such work can vary, FDA estimates that the custom software in use has a limited scope of application, and an average of 60 hours of work by the laboratory supervisor would be required to validate custom software at a facility. Detailed presentations of these assumptions are provided in section 2.4.3 of the background reports by FDA and ERG.

The last requirement for the quality control program is for procedures that stipulate how the quality program should be operated. Industry consultants indicate that facilities have quality systems in place, but that most facilities are not aware of some minor elements that should be included in the procedures. Consequently, inspectors for accreditation groups often find a few deficiencies during initial visits. FDA estimates that about 95 percent of eye banks, 23 percent of conventional tissue, and up to 80 percent of stem cell facilities, sperm banks and ART facilities will have minor deficiencies that would require them to revise one minor and one major procedure. In addition, FDA estimates that 5 percent of all eye banks, conventional tissue, reproductive tissue facilities, and industry non-compliant stem cell facilities, may identify major deficiencies, and would need to prepare five minor procedures and one major procedure to address those problems.

The agency further assumes that facilities may generally need to do some additional quality control work to comply with the quality control program requirements in the CGTP rule. Although some tasks would not take any additional time to perform, FDA estimates that one additional hour per month each for the laboratory director and supervisor may be needed. FDA estimates that 95 percent of all eye banks, 23 percent of conventional tissue banks and approximately 80 percent of stem cell facilities and reproductive tissue facilities would allocate this additional staff time.

d. *Section 1271.170—organization and personnel.* The proposed rule would require facilities to employ sufficient personnel with the necessary education and experience to complete their tasks. Personnel would be trained to perform their work adequately. The EBAA, AATB, FAHCT, and AABB standards for quality assurance all include provisions for appropriate personnel qualifications and training, and recordkeeping related to this requirement. It is expected that most facilities for eye banking, conventional tissue banking, and stem cell production already follow these practices as proposed. The fraction of facilities in conventional tissue and stem cell manufacturing that do not follow industry standards would incur new costs. Similarly, 5 percent of the facilities in the reproductive tissue industries would incur some new costs associated with hiring staff that meet formal training requirements. The cost of this staffing effort is estimated to be approximately $15,560 per affected facility.

FDA anticipates that the 23 percent of conventional tissue facilities, 95 percent of industry-noncompliant stem cell facilities, 5 percent of sperm banks, and 5 percent of small ART facilities would incur new training costs in complying with the proposed rule. For a small tissue establishment, these costs are estimated to average $2,348. The proposed CGTP would also require that records of personnel qualifications and training be maintained, but because the incremental record keeping is minimal, FDA assumes that the cost to comply with this requirement would be negligible. Detailed presentations of these assumptions are provided in section 2.4.4 of the background reports by FDA and ERG.

e. *Section 1271.180—procedures: general requirements.* The proposed rule would require establishments to keep written procedures for all steps performed during manufacturing of human cellular or tissue-based products, and to perform an annual review. FDA anticipates a negligible incremental cost for most facilities following industry standards, and an additional 120 hours by the laboratory director for facilities not following the current industry standards. FDA estimates that 5 percent of eye banks would need to expand their current review efforts, and that 23 percent of conventional tissue banks, 95 percent of stem cell facilities, and 50 percent of reproductive tissue facilities would incur new costs for an annual review.

f. *Section 1271.190—facilities.* The proposed rule stipulates a number of requirements regarding the construction of facilities, covering size, location, lighting, ventilation, plumbing, drainage, and toilet and washing facilities. The facility would also be required to have properly divided areas for appropriate quality control. Cleaning requirements are also outlined, including requirements for written procedures and schedules for cleaning and documentation of cleaning activities. Based on discussions with industry experts, FDA estimates that nearly all facilities that follow industry standards would not incur new costs under the proposed CGTP rule. However, some establishments that generally adhere to cleaning standards do not have written procedures. FDA

estimates that 5 percent of all eye banks, in addition to 23 percent of the conventional tissue banks, 95 percent of all stem cell facilities, and 5 percent of reproductive tissue facilities would incur the cost of writing a minor procedure for cleaning. The facilities provision of the CGTP also would require that records of cleaning be maintained. This proposed requirement is currently practiced by most facilities, and is expected to have a negligible impact on facilities not following industry standards.

g. *Section 1271.195—environmental control and monitoring.* The proposed rule would require that procedures be written for environmental control and monitoring activities or systems where an environmental condition could have an adverse effect on the human cellular or tissue-based product. The rule also would require that environmental control systems be regularly inspected and that control and monitoring activities be documented. The impact of this provision of the CGTP varies by industry sector. For eye banking, the EBAA standards already contain relevant provisions, however, some additional costs may be incurred for annual inspection of the environmental control systems and for keeping records of environmental control and monitoring activities. It is estimated that 5 percent of eye banks may incur new costs for inspection and certification of equipment. FDA anticipates that the conventional tissue facilities following AATB standards would experience no new costs, but that the remaining 23 percent of facilities would need to prepare a minor procedure to control and monitor ventilation and air filtration.

The current FAHCT and AABB standards do not provide for written procedures for environmental control and monitoring. FDA therefore estimates that 95 percent of all stem cell facilities would need to develop a minor procedure to control and monitor ventilation and air filtration to comply with the CGTP. However, because the industry standards provides for appropriate environmental controls, FDA assumes that some facilities are currently performing control activities. The agency estimates that as many as half of the facilities currently following standards may already be conducting routine inspections of their environmental control equipment. It is assumed that the remaining 50 percent of those facilities, and 95 percent of facilities assumed not to be following industry standards, would incur additional costs to inspect equipment and perform recordkeeping related to environmental control.

The agency also assumes that most reproductive tissue facilities would need to prepare written procedures, and do additional recordkeeping in compliance with the CGTP. FDA estimates that 80 percent of all sperm banks and ART facilities would incur costs to comply with this provision of the proposed rule. FDA also estimates that 20 percent of ART facilities would increase ventilation systems inspection activities. Table 2 provides estimates of cost per facility associated with these efforts.

h. *Section 1271.200—equipment.* The proposed rule stipulates that appropriate equipment be used and any equipment used be validated. Cleaning, maintenance, and calibration of equipment would be performed according to established schedules and procedures; equipment would be regularly inspected for adherence to applicable procedures and schedules; and all such activities would be documented. In addition, facilities would be required to keep records of each use of each piece of equipment, including the identification of each human cellular or tissue-based product manufactured with that piece of equipment.

The standards related to equipment, as specified by AATB, EBAA, FAHCT, and AABB generally address maintenance procedures, and recordkeeping related to maintenance. However, the proposed rule extends beyond the industry standard for EBAA, FAHCT and AABB in the areas of equipment inspection and recordkeeping. FDA therefore estimates that 95 percent of all eye banks would allocate an additional half-hour per month for the laboratory supervisor to inspect equipment, an additional half hour per month of technician time to documenting equipment cleaning and calibration, and two additional hours of technician time per month in recording each use of the equipment.

The estimated 23 percent of conventional tissue facilities that currently do not follow AATB standards would also incur new costs related to equipment quality control. FDA estimates that small facilities would prepare one minor procedure for calibration, and for cleaning and other maintenance for each of six pieces of equipment. In addition, small facilities will allocate an additional hour per month of lab supervisor time for routine inspection of equipment, an additional hour per month of technician time for documentation of cleaning and calibration, and 4 hours per month recording each use of the equipment. FDA estimates large facilities would write minor procedures for each of eight pieces of equipment, and would allocate an additional 2 hours per month of lab supervisor time for routine inspection of equipment, an additional 2 hours per month of technician time to record cleaning and calibration activities, and an additional 8 hours of technician time per month to record each use of each piece of equipment. It is anticipated that the facilities simultaneously preparing multiple procedures related to equipment would realize some economies of scale because of similarities across procedures. This is expected to result in a savings of 30 percent in the total amount of staff time to prepare six to eight equipment maintenance procedures at one time.

Stem cell facilities also would be expected to perform some additional work to align current practice with the proposed CGTP requirements. Current FAHCT procedures provide for routine maintenance and calibration of equipment. In addition, the AABB standards recommend that standard operating procedures (SOP's) be established for proper equipment maintenance and monitoring. To further develop procedures to address routine maintenance and recordkeeping under the proposed CGTP, FDA estimates that 95 percent of all stem cell facilities would prepare a minor procedure for calibration of each of six pieces of equipment. In addition to the preparation of procedures, lab personnel would carry out the maintenance work, estimated to require an additional half hour of supervisor time per month in routine inspection of equipment, an additional half hour per month for technicians to document cleaning and calibration work, and an added 4 hours per month of technician time to record each use of equipment. In addition, most stem cell facilities that do not currently follow FAHCT or AABB standards would incur the cost of preparing a minor procedure for cleaning, for sanitizing and for routine maintenance of six pieces of equipment.

In the reproductive tissue industry, the agency estimates that all facilities have the appropriate equipment to process the tissue products, but that only a small percentage currently conduct recordkeeping and have written procedures related to maintenance, calibration and other activities as specified under the proposed CGTP. The agency estimates that 90 percent of sperm banks and ART facilities would develop additional procedures, and that 100 percent of these facilities would need to perform additional

recordkeeping related to equipment use. In addition, an estimated 5 percent of sperm banks, and 50 percent of ART facilities would devote additional resources to routine calibration of equipment. An estimated 5 percent of facilities would need to also increase efforts in routine inspection, and record keeping related to equipment cleaning and maintenance. The costs per facility associated with each of these areas of activity are presented in table 2. Section 2.4.8 of the ERG background paper provides a detailed presentation of these assumptions.

i. *Section 1271.210—supplies and reagents.* The proposed rule would require that procedures be established for receipt of supplies and reagents used in the manufacture of human cellular and tissue-based products. In particular, manufacturers would be required to verify that supplies and reagents meet specifications designed to prevent transmission of communicable disease and impairment of product function and integrity. Verification of supply or reagent quality could be accomplished with a certificate of analysis. The proposed rule would also require documentation of receipt, verification, and each use of a supply or reagent in product processing.

The existing industry standards address some or all of these activities, and the estimated impact per facility varies accordingly. EBAA standards specify that sterilized supplies and reagents should contain sterilization dates, method or appropriate expiration dates. However, the agency estimates that up to 95 percent of eye banks would be required to develop additional procedures related to receipt and verification, and would devote additional staff time to recording the receipt of supplies and reagents. Similarly, FAHCT and AABB standards contain provisions for quality control in the storage, handling and use of supplies and reagents, including maintenance of records. However, FDA expects that approximately 95 percent of stem cell facilities may be required to expand on their current SOP's and recordkeeping in order to comply with the CGTP provisions.

The current AATB standards address most of the requirements for supplies and reagents included in the proposed rule. FDA assumes that the estimated 23 percent of facilities that follow these standards would be required to prepare additional procedures for in-house reagent verification, for receipt and verification, and would devote additional staff time to keeping records of the receipt of supplies and reagents.

Based on consultant estimates that 95 percent of commercial sperm banks follow AATB guidelines, the agency estimates that only 5 percent of sperm banks and 80 percent of ART facilities would need to take new steps to comply with this proposed CGTP provision. For these facilities, the agency anticipates that each facility would need to prepare new procedures for receipt and verification of supplies and reagents, and each will devote additional staff time to recording the receipt of these materials. The estimated costs per facility are presented in table 2.

j. *Section 1271.220—process controls.* The proposed rule would require facilities to monitor manufacturing processes to ensure that specified requirements for the product are met. This includes having written procedures for the use and removal of processing material that can damage products, and procedures for in-process monitoring. The standards for tissue banking specified by the AATB include activities to address these process controls, but the EBAA, FAHCT, and AABB standards do not include specific requirements for monitoring and removal of processing material that may damage the product. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, 95 percent of stem cell facilities, and 90 percent of sperm banks and ART facilities would need to prepare a minor procedure related to monitoring and removal of damaging processing material. Consultants estimate that most reproductive tissue facilities have procedures for in-process monitoring, and in these industries, an estimated 5 percent of reproductive tissue facilities would need to prepare procedures to address this activity.

k. *Section 1271.225—process changes.* The proposed regulation would require establishments to institute process change procedures that will govern modifications to established operations. Changes to processes would be documented with the date of the change, the date of implementation, the rationale for the change, and appropriate approval signatures. The current standards for AATB, FAHCT and the AABB provide for SOP's for process changes, although recordkeeping procedures are not specified. Current EBAA standards do not provide for SOP's for process changes. FDA therefore estimates that nearly all eye banks would be required to prepare a major procedure for process changes, and would allocate an additional half hour of lab director time to document process changes.

FDA anticipates that conventional tissue banks not following the AATB standard would need to prepare a major procedure related to process changes, and nearly all tissue banks would increase related recordkeeping. The agency estimates that small conventional tissue banks would spend an additional half hour per month of lab director time to document process changes, and large facilities would allocate an additional hour of lab director time for this. FDA anticipates that almost all stem cell facilities that do not follow FAHCT or AABB standards would need to prepare a major procedure to address process changes. In addition, FDA estimates that 95 percent of all stem cell facilities would allocate an additional half hour of laboratory director time to document process changes.

According to industry contacts, most sperm banks already have established written procedures for process changes, and would therefore be in compliance with this proposed provision. FDA is also informed that ART facilities follow standards for process changes, but the procedures may not be in writing. In addition, industry consultants estimate that many reproductive tissue facilities may not keep written records of their process changes. Based on these characterizations, FDA estimates that approximately 5 percent of sperm banks and 90 percent of ART facilities would need to develop a written procedure for process changes. In addition, the agency estimates that 90 percent of sperm banks and ART facilities would need to allocate additional staff time (an estimated one half-hour per month at small facilities and one hour per month at large facilities) to record changes. The associated costs per facility are presented in table 2.

l. *Section 1271.230—process validation.* The proposed rule would require facilities to validate processes that cannot be verified through subsequent inspection and testing. Current EBAA standards do not require process validation. Although current AATB, FAHCT, and AABB standards include provisions for process validation and related recordkeeping, industry experts indicate that additional validation work would be required at nearly all facilities under the proposed rule. FDA therefore estimates that 95 percent of all eye banks, of all conventional tissue banks and all stem cell facilities, not compliant with AABB or FAHCT, would need to prepare two major procedures related to process validation, and 95 percent of conventional tissue banks and AABB/FAHCT-compliant stem cell facilities

would need to revise two major procedures. FDA estimates that 95 percent of all facilities in the tissue industry would devote additional staff time for process validation.

In addition to the initial validation work, CGTP would require revalidation of procedures. The agency estimates that 95 percent of eye banks, conventional tissue banks and stem cell facilities would need to allocate an additional amount (on the order of 20 to 40 hours) of laboratory staff time for annual revalidation.

Reproductive tissue industry consultants considered that the process validation requirement would have limited application to this industry because the tissues involved in laboratory processes (e.g., sperm and ova) are not uniform in quality. However, quality control through in-process monitoring (under § 1271.220) would be applicable to these tissues.

m. *Section 1271.250—labeling controls; procedures.* The proposed rule would require facilities to establish and maintain written procedures for controlling the labeling of products. The procedures would ensure proper identification of products and include various checks and verifications. Each product would also be accompanied by donor suitability information, if applicable. Other labeling requirements would also be met, such as labeling products appropriately with the required information.

According to consultants and industry contacts, labeling controls are usual and customary practice in the industry. FDA anticipates that only about 5 percent of all facilities in eye banking, in conventional tissue banking, in stem cell processing and in the reproductive tissue industries would need to do additional work to comply with the proposed labeling controls. FDA estimates that such facility would need to revise a major procedure for proper identification of products.

n. *Section 1271.260—storage.* The proposed rule would require that storage areas be controlled to prevent mix-ups and contamination. Temperature should be monitored and limits established, including expiration dating where appropriate. Each of the relevant industry standards contains provisions regarding storage practices. Based on agency review of current industry standards, and conversations with experts about current practices at facilities, FDA anticipates that virtually all facilities follow industry standards that would comply with this provision of the proposed CGTP. These provisions of the proposed rule are therefore expected to produce no new cost impact for facilities in eye banking, conventional tissue banking, stem cell processing, and reproductive tissue.

o. *Section 1271.265—receipt and distribution.* The proposed rule would require that procedures be established and maintained for receiving, rejecting, distributing, and disposing of human cellular or tissue-based products. Documentation of each of those activities, when performed, would also be required. Packaging and shipping containers would be validated and appropriate shipping conditions must be defined. Procedures would also be established to determine whether products returned to an establishment are suitable to be returned to inventory. Agency review of current industry standards indicates that provisions related to this area of quality control, except for package validation, are included in each of the relevant standards.

The primary impact of the proposed CGTP provisions for product receipt and distribution thus involves packaging validation for most facilities, and procedures development for facilities that do not currently follow industry standards. FDA estimates that 95 percent of eye banks, conventional tissue banks and stem cell facilities would allocate approximately 4 extra hours per month for a laboratory technician to validate packaging, particularly packaging changes. In addition, an estimated 5 percent of eye banks, conventional tissue banks, and stem cell facilities would increase lab supervisor time to document receipt of products.

The agency estimates that conventional tissue banks not following AATB standards would need to revise one major procedure for receiving products, revise one major procedure related to distribution of products, and prepare a minor procedure for return of products to inventory. FDA estimates that 95 percent of stem cell facilities would need to write one major procedure addressing receiving activities. Facilities following FAHCT or AABB standards would also need to revise a major procedure for product distribution, while all other facilities would need to prepare a new major procedure for product distribution as well as a minor procedure for handling of products returned to inventory.

According to industry contacts, most sperm banks and ART facilities have a protocol for receiving and distributing reproductive tissue products, however, an estimated 5 percent of facilities would need to write a major procedure for receiving activities and one for distribution. Similarly, an estimated 5 percent of facilities do not currently follow industry standards for product documentation. The agency estimates that an additional 4 to 8 hours of staff time per month would be required by those facilities, for documentation activities. Industry consultants indicate that although most reproductive tissue facilities utilize "dry shippers" for shipped products, most do not perform formal packaging validation. FDA therefore estimates that all facilities would be required to perform packaging validation, in compliance with the proposed CGTP. Experts in the reproductive tissue industry also consider it unusual for a product to be returned to inventory; given the potential risk of product deterioration or damage. It is expected that most sperm banks already have a formal procedure for handling returned product, and that ART facilities generally have an established protocol, but not a written procedure. The agency estimates that approximately 5 percent of sperm banks and 100 percent of ART facilities therefore would be required to write a minor procedure to comply with this proposed CGTP requirement. The costs per facility for these activities are presented in table 2.

p. *Section 1271.270—records.* The proposed rule would require that records be maintained for any significant step in the manufacturing process. A records management system would need to be in place and procedures would need to be established for keeping records associated with donor suitability record keeping requirements. Records would be maintained for at least 10 years. The proposed rule would also require that records be kept of any contracts or agreements. Although many components of the required recordkeeping system are addressed under separate provisions of the proposed CGTP, there may be a few minor gaps in the records system of a facility that would be addressed under this general provision. FDA therefore estimates that approximately 95 percent of all eye banks, conventional tissue banks, and stem cell facilities that follow FAHCT or AABB standards, would be required to write at least one minor procedure, and revise one major procedure related to recordkeeping.

The agency also estimates that additional lab director time would be allocated (estimated 40 hours at small facilities and 80 at large facilities) to set up enhanced recordkeeping where a system is already in place. System enhancement would be performed at an estimated 95 percent of eye banks, 23 percent of conventional tissue facilities.

95 percent of stem cell facilities, 5 percent of sperm banks, and 50 percent of the ART facilities.

Various industry standards specify record retention, although the time periods vary somewhat. Of those facilities following industry standards, approximately 95 percent of eye banks and the 77 percent of conventional tissue banks retain records for at least 10 years, and the remainder retain records for a minimum of 5 years. For these facilities, and the stem cell facilities that do not currently follow industry standards, FDA estimates increased record retention costs based on the cost of storing an additional 5 boxes (2.4 cubic feet each) of records per year for 5 years. The retention standards of FAHCT and AABB for records related to products are different from those concerned with facility and equipment maintenance and personnel training. All records related to the product should be retained indefinitely and records related to facility and equipment maintenance and personnel training should be retained for only 5 years.

FDA estimates that a half of the records at stem cell facilities following industry standards would need to be retained for an additional 5 years, and the annual cost will be comparable to that of other small tissue facilities. The agency also estimates that nearly all stem cell facilities that are not following industry standards will increase record retention. Almost all stem cell facilities that do not follow industry standards would be required to prepare at least one minor procedure and to revise a major procedure related to record keeping. The laboratory director at these facilities would be expected to allocate 40 hours of time to improving the facility's current recordkeeping system.

Consultants estimate that within the reproductive tissue industries all facilities have some record management system, and many facilities have systems that meet the requirements of the proposed rule. Consultants estimate that most sperm banks and the currently accredited ART facilities have adequate records management systems in place, but that approximately 5 percent of sperm banks, and about 50 percent of the ART facilities would need to allocate additional laboratory staff time (i.e., 40 hours at small facilities and 80 hours at larger facilities) to enhance their current recordkeeping system in compliance with the proposed rule.

In addition, FDA is informed that the usual and customary practice in most ART facilities is to retain donor records for an indefinite period. Usual and customary practice in sperm banks is to retain records for at least 15 years, thus more than the 10-year period specified in the proposed rule. It is estimated that only 5 percent of sperm banks and ART facilities would need to extend record retention by an estimated 5 years. The additional cost of storing these files is based on an assumption of 5 boxes (each approximately 2 cubic feet) accumulated per year at small facilities, and 10 boxes per year at large facilities, for an additional 5 years, at a cost of 30 cents per cubic foot per year. The estimated costs per affected facility are summarized in table 2.

q. *Section 1271.290—tracking.* The proposed rule stipulates the steps needed to properly track a product from donor to recipient and vice versa. The proposed CGTP would require that facilities maintain a method for product tracking and that each product be assigned and labeled with a unique identifier. If a new identifier is assigned during the manufacturing process, procedures would be required for relating the new identifier to the old identifier. Records of product transfers would be kept in the recipient's medical records. The facility that manufactured the product would also keep track of the disposition of each product, so that the recipient of the product can be easily identified. Facilities would be required to inform consignees of the established tracking method and would be required to document that consignees agreed to participate in their tracking method.

Product "traceability" is a familiar concept and common practice in eye banking, in conventional tissue banking, and in the stem cell processing industry. Eye banks following EBAA standards maintain records with information that permits tracing of product from the donor source to the patient recipient, working through the surgeon who performed the procedure. FDA anticipates that only 5 percent of eye facilities would need to enhance current tracking, and would be required to prepare one major procedure related to product tracking, spend additional staff time each month to identify and document recipient information, and would allocate additional laboratory director time to institute agreements for information sharing with the consignees who will receive products.

Conventional tissue facilities following AATB standards are able to trace all products from donation source to product recipient. Conventional tissue facilities not following AATB requirements would be required to revise a major procedure to address product tracking, allocate additional staff time each month to obtain and record information about product recipients, and allocate some additional laboratory director time (on a one-time basis) to institute formal contracts with consignees. The FAHCT and AABB standards for product tracking in stem cell facilities recommend that the facility be able to trace products to final distribution or disposition, but do not specify that formal agreements be established with consignees to assure timely tracking of products. FDA therefore estimates that 95 percent of stem cell facilities would, on a one-time basis, allocate an additional 20 hours of laboratory supervisor time to institute agreements for information sharing with the consignees who will receive products. In addition, FDA estimates that 95 percent of stem cell facilities that are not following FAHCT or AABB standards would need to revise a major procedure related to product tracking, and would need to allocate additional staff hours each month for recipient identification and documentation.

Consultants for the reproductive tissue industry indicate that although sperm banks and ART facilities generally perform product tracking and adhere to the practice of documenting recipient information for products, current practices in assigning and documenting products with unique identifiers throughout tissue processing may widely vary, and there may be little documentation of tracking agreements with consignees. Most reproductive tissue facilities therefore would need to review current systems and perform some enhancements. It is estimated that 80 percent of reproductive tissue facilities would need to revise a major procedure related to product tracking, and would allocate additional staff hours each month for recipient identification and documentation. In addition, approximately 80 percent of facilities would need to allocate lab supervisor time to institute agreements for information sharing with the consignees who will receive products. The estimated cost per facility to perform these activities are presented in table 2.

Hospitals generally handle all categories of cellular and tissue-based products. For accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), organizations that store tissue must keep records that permit tracing of any tissue from the donor or source facility to all recipients or other final dispositions. The records must include documentation of tissue use in the patient's clinical record. Most hospitals are accredited and, therefore, are presumed to be tracking tissue to recipient. We believe that hospitals not accredited tend to be specialized

facilities not handling cellular and tissue-based products. Because we know of no hospital receiving tissues and not currently tracking tissue to recipient, we expect hospitals to incur no additional costs as a result of this regulation. However, as some of our sources (Ref. 45) lack conclusive data on the adequacy of hospital recordkeeping, we welcome comment on this matter.

The proposed rule would also require that specimens of dura mater be archived for the appropriate duration under appropriate conditions to enable future testing for evidence of TSE. FDA recommends that the specimens be archived for 16 years beyond the expiration date. As CDRH guidance already recommends that such specimens be archived for 10 years, this requirement would not impose an additional tracking burden. FDA assumes the incremental cost of the longer storage time to be extremely small and the overall cost impact to be negligible.

r. *Section 1271.320—complaint file.* The proposed rule would require facilities to maintain procedures for reviewing and evaluating complaints and to maintain a file for these complaints. Facilities would be required to review and evaluate complaints and to determine whether each complaint represents an event that should be reported to FDA. Documentation of the review and evaluation would be required, even if no investigation is made. FDA finds that the AATB, FAHCT, and AABB standards explicitly address procedures or recordkeeping related to complaints. Based on discussions with industry experts, the agency assumes that nearly all facilities currently track, albeit informally, the complaints received from consignees and recipients. Facilities that would be required to prepare written procedures for handling complaints, and to review complaints on a yearly basis, would incur additional costs. The agency estimates that additional costs for facilities to maintain a complaint file would be negligible.

To fully comply with provisions in the proposed rule, FDA estimates that 95 percent of all eye banks would revise a minor procedure to include the required handling of complaints, and would allocate some additional staff time each year to review complaints. FDA assumes that conventional tissue facilities following AATB standards would already perform the necessary activities, but the estimated 23 percent of facilities not following AATB standards would need to prepare a minor procedure for complaint handling, and would allocate additional laboratory director time each year to review complaints that are received.

Although the industry standards for stem cell processing provide that records be maintained of both donor and recipient complaints, the proposed rule requires that facilities also have written procedures for complaint review. FDA therefore estimates that 95 percent of all stem cell facilities would be required to write a minor procedure to handle complaints, and that 95 percent of all facilities would also be required to allocate additional time for yearly review and handling of complaints.

Consultants assessing the impact of the proposed rule on the reproductive tissue industry estimate that about 95 percent of sperm banks and ART facilities already have written procedures for dealing with complaints, and that 5 percent of facilities would need to prepare a minor procedure for complaint handling, and would allocate additional laboratory director time each year to review complaints that are received. The estimated costs per affected facility are presented in table 2.

s. *Section 1271.350—reporting.* The proposed rule would require facilities to review adverse reaction reports and report any adverse reactions, or product deviations, involving transmission of disease, or of the failure of a product that is fatal, life-threatening, results in permanent impairment of the body, or requires surgical intervention. Based on expert assessments of current industry practices, and the inclusion of adverse event reporting in current industry standards, the agency expects that this requirement, within the proposed CGTP framework for quality management, would impose a negligible cost on facilities in the industry.

t. *Section 1271.370—labeling and claims.* The proposed rule would require that products be labeled clearly and accurately, with information including name and address of the manufacturer, a description of the product, and product expiration date. The storage temperature, warnings, and instructions would be required on the label or on a package insert. The rule would also require that any claims on labeling be truthful and that any therapeutic claim or claim of a clinical outcome of a product would be subject to regulation under section 351 of the PHS Act and/or the act.

Industry consultants inform FDA that such elements are typically present on the labels of products manufactured by eye banks, conventional tissue banks, stem cell facilities, sperm banks and ART facilities. Proper labeling is considered very important to these industries, to prevent misuse of the product. In addition, these industries generally do not make therapeutic or related claims for their products. FDA assumes, therefore, that the industry would be in compliance with this provision of the proposed CGTP rule, and estimates that the cost impact would be negligible.

u. *Section 1271.400—inspections.* FDA could conduct inspections of any facility subject to the proposed CGTP rule. FDA would interact primarily with one responsible person for each establishment, but other personnel may also be involved in the inspection. FDA could inspect facilities, equipment, processes, products, procedures, labeling, and records, and could review and copy any records required to be kept under the proposed rule. The agency estimates that all industry facilities would be subject to this provision of the proposed CGTP, and that inspections would occur annually. FDA estimates that up to 16 hours of laboratory technician time could be necessary, to accompany the FDA inspector through the facility and to support the inspector's information needs, and that up to 4 hours of laboratory director time would be needed for activities related to the inspection. This is expected to yield a cost of approximately $702 per facility.

v. *Section 1271.420—human cellular and tissue-based products offered for import.* The proposed rule would require importers of human cellular and tissue-based products to notify the FDA district director having jurisdiction over the port of entry through which the product is imported or offered for import. The product would be held intact until it is inspected and released by FDA.

In the cellular and tissue-based product industries there is currently very little use of imported tissue that would trigger activities for facility compliance with this provision of the proposed CGTP. FDA therefore estimates the current cost for industry compliance with this proposed requirement would be negligible.

w. *Section 1271.440—orders of retention, recall, and cessation of manufacturing.* Industry firms could incur costs to comply with orders under this proposed provision. There is little available data on which to base estimates of the future frequency and scope of tissue industry conditions and practices that would necessitate such actions on the part of FDA. The agency anticipates that product orders under this provision would be rare. FDA estimates that the yearly costs to

industry resulting from such orders would therefore be negligible.

3. Summary of One-Time and Yearly Cost Impacts

The costs for each subsection of the proposed rule are the product of the estimated number of affected establishments in the industry (table 1), the establishment noncompliance rate by CGTP provision, by industry sector, and the compliance cost per establishment (table 2). Total compliance costs, summed by provision of the proposed rule, are presented by sector in tables 4 through 8. The aggregate compliance costs for all tissue industries are summarized in table 9. The total annualized costs presented in these summary tables include the reported one-time costs, such as are incurred to prepare new procedures, annualized over 10 years using a 7 percent discount rate.

TABLE 4.—AGGREGATE COMPLIANCE COSTS FOR EYE BANKS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$122,111	$457,459	$474,845
1271.170	Organization and personnel	$0	$0	$0
1271.180	Procedures—General requirements	$0	$47,196	$47,196
1271.190	Facilities	$1,701	$0	$242
1271.195	Environmental control and monitoring	$0	$23,245	$23,245
1271.200	Equipment	$0	$109,816	$109,816
1271.210	Supplies and reagents	$10,776	$17,545	$19,079
1271.220	Process Controls	$70,124	$0	$9,984
1271.225	Process changes	$75,593	$44,836	$55,599
1271.230	Process validation	$321,218	$85,016	$130,750
1271.250	Labelling Controls—Procedures	$1,989	$0	$283
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$0	$145,008	$145,008
1271.270	Records	$369,032	$103	$52,644
1271.290	Tracking	$11,845	$9,302	$10,989
1271.320	Complaint file	$10,776	$59,782	$61,316
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$80,712	$80,712
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$995,165	$1,080,020	$1,221,708

TABLE 5.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE FACILITIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$77,800	$137,655	$148,732
1271.170	Organization and personnel	$393,668	$63,751	$119,801
1271.180	Procedures—General requirements	$0	$209,484	$209,484
1271.190	Facilities	$8,544	$0	$1,216
1271.195	Environmental control and monitoring	$8,544	$5,030	$6,247
1271.200	Equipment	$79,352	$62,969	$74,267
1271.210	Supplies and reagents	$17,088	$5,030	$7,463
1271.220	Process Controls	$21,128	$0	$3,008
1271.225	Process changes	$25,169	$53,096	$56,679
1271.230	Process validation	$268,024	$164,065	$202,226
1271.250	Labelling Controls—Procedures	$2,736	$0	$390
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$33,713	$146,448	$151,248
1271.270	Records	$172,967	$455	$25,082
1271.290	Tracking	$47,498	$101,347	$108,110
1271.320	Complaint file	$8,544	$17,140	$18,356

TABLE 5.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE FACILITIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$77,880	$77,880
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$1,164,775	$1,044,350	$1,210,189

TABLE 6.—AGGREGATE COMPLIANCE COSTS FOR STEM CELL INDUSTRIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$188,166	$473,119	$499,909
1271.170	Organization and personnel	$739,100	$111,530	$216,761
1271.180	Procedure—General requirements	$0	$393,300	$393,300
1271.190	Facilities	77,983	$665,000	$676,103
1271.195	Environmental control and monitoring	$77,983	$202,323	$213,426
1271.200	Equipment	$387,080	$434,198	$489,309
1271.210	Supplies and reagents	$113,430	$7,695	$23,845
1271.220	Process Controls	$260,336	$0	$37,066
1271.225	Process changes	$33,155	$108,158	$112,878
1271.230	Process validation	$625,670	$275,619	$364,700
1271.250	Labeling Controls—Procedures	$4,799	$0	$683
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$446,405	$26,520	$90,078
1271.270	Records	$161,856	$2,880	$25,925
1271.290	Tracking	$377,103	$155,040	$208,731
1271.320	Complaint file	$77,983	$144,210	$155,313
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$194,700	$194,700
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$3,571,049	$3,194,292	$3,702,727

TABLE 7.—AGGREGATE COMPLIANCE COSTS FOR ART[1] FACILITIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$272,904	$586,854	$625,709
1271.170	Organization and personnel	$256,740	$25,358	$61,912
1271.180	Procedures—General requirements	$0	$1,366,200	$1,366,200
1271.190	Facilities	$5,909	$621,600	$622,441
1271.195	Environmental control and monitoring	$94,536	$146,342	$159,802
1271.200	Equipment	$767,022	$583,549	$692,756
1271.210	Supplies and reagents	$94,536	$3,596	$17,056
1271.220	Process Controls	$115,834	$0	$16,492
1271.225	Process changes	$341,302	$165,434	$214,028
1271.230	Process validation	$0	$0	$0
1271.250	Labeling Controls-Procedures	$9,481	$0	$1,350
1271.260	Storage	$0	$0	$0

TABLE 7.—AGGREGATE COMPLIANCE COSTS FOR ART[1] FACILITIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.265	Receipt and distribution	$335,612	$36,230	$84,014
1271.270	Records	$612,720	$400	$87,637
1271.290	Tracking	$516,010	$0	$73,468
1271.320	Complaint file	$5,909	$12,254	$13,096
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$233,640	$233,640
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$3,428,515	$3,781,457	$4,269,601

[1]Assisted Reproductive Technology

TABLE 8.—AGGREGATE COMPLIANCE COSTS FOR SPERM BANKS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$12,105	$23,661	$25,384
1271.170	Organization and personnel	$15,560	$2,348	$4,563
1271.180	Procedures-General requirements	$0	$82,800	$82,800
1271.190	Facilities	$299	$28,000	$28,042
1271.195	Environmental control and monitoring	$4,776	$6,592	$7,272
1271.200	Equipment	$25,522	$26,286	$29,920
1271.210	Supplies and reagents	$299	$162	$204
1271.220	Process Controls	$5,722	$0	$815
1271.225	Process changes	$698	$7,452	$7,551
1271.230	Process validation	$0	$0	$0
1271.250	Labeling Controls-Procedures	$349	$0	$50
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$12,575	$1,632	$3,422
1271.270	Records	$2,760	$18	$411
1271.290	Tracking	$27,664	$0	$3,939
1271.320	Complaint file	$299	$552	$594
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$14,160	$14,160
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$108,628	$193,663	$209,127

TABLE 9.—SUMMARY OF AGGREGATE COMPLIANCE COSTS FOR ALL TISSUE INDUSTRIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$673,085	$1,678,748	$1,774,580
1271.170	Organization and personnel	$1,405,068	$202,987	$403,038
1271.180	Procedures—General requirements	$0	$2,098,980	$2,098,980
1271.190	Facilities	$94,435	$1,314,600	$1,328,046
1271.195	Environmental control and monitoring	$185,839	$383,532	$409,991
1271.200	Equipment	$1,258,976	$1,216,819	$1,396,069
1271.210	Supplies and reagents	$236,129	$34,028	$67,648

TABLE 9.—SUMMARY OF AGGREGATE COMPLIANCE COSTS FOR ALL TISSUE INDUSTRIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.220	Process Controls	$473,145	$0	$67,365
1271.225	Process changes	$475,917	$378,976	$446,735
1271.230	Process validation	$1,214,911	$524,700	$697,675
1271.250	Labelling Controls—Procedures	$19,354	$0	$2,756
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$828,305	$355,838	$473,770
1271.270	Records	$1,319,336	$3,856	$191,700
1271.290	Tracking	980,120	265,690	405,237
1271.320	Complaint file	$103,510	$233,937	$248,675
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$601,092	$601,092
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$9,268,130	$9,293,783	$10,613,357

B. Estimated Benefits of the Proposed Rule

The overall purpose of the CGTP rule is to prevent the introduction, transmission, or spread of communicable disease through the use of human cellular and tissue-based products. Although industry quality standards exist for most of the affected products, not all members of the industry follow these standards. FDA finds that public safety cannot be assured or effectively protected through reliance on this less formal and voluntary mechanism for quality assurance. The existing industry standards vary to some extent in their comprehensiveness. Moreover, there are variations in the extent to which the industry follows these standards.

For example, most industry consultants for the cost analysis agree that quality standards, such as those proposed by the FDA, and similar standards recommended by industry, could substantially reduce the risk of product contamination and product failure. However, most experts also opined that, because additional costs are associated with maintaining higher quality standards, and because there is no explicit patient demand for higher quality standards to prevent contamination risks, some facilities are not currently following adequate quality control standards. A regulatory requirement for quality systems would provide the incentive needed to bring all facilities to a more uniform and appropriately high standard of quality.

The primary beneficiaries of the proposed CGTP rule would be the patients who receive the cellular and tissue-based products. Benefits to patients would result from the reduced risk of communicable disease by avoiding product contamination or product failure through CGTP. The discussion that follows considers the potential benefit of avoided problems with tissue products, based on a survey of the clinical literature.

Recent clinical literature indicates that each type of tissue product considered in the proposed rule has documented contamination or other product problems resulting from processing, or other steps in manufacturing. These reported quality problems provide a basis for assessing the magnitude of the potential benefit from further reducing events that increase the risk of communicable disease transmission. In cases involving eye tissue, conventional tissue, or stem cell products, problems have required medical intervention to treat infection, or to replace an implanted defective product. In some clinical applications, product failures have increased the risk of patient mortality. In other applications, such as embryo processing, poor product quality is associated with lower success rates (i.e., pregnancy rates) among treated patients, which results in an increase in transfer attempts. In general, FDA anticipates that the risk of communicable disease transmission from product quality problems will decline as a result of compliance with the proposed CGTP.

The sections that follow describe product-related problems associated with communicable disease transmission that are at least partly attributable to a lack of uniform quality standards in manufacturing. The costs related to correcting these problems are considered, in order to gauge the potential magnitude of the benefits associated with improved quality in manufacturing. The discussion is organized by types of tissue product.

1. Eye Tissue Products

Primary corneal graft failure is a key adverse outcome of concern following corneal tissue transplant. Such failures result in additional graft attempts. Each attempt increases the risk of communicable disease transmission by exposing the recipient to another tissue product and to another surgical procedure. Although primary corneal graft failure is relatively uncommon, its occurrence has been attributed to several factors related to tissue collection, processing and product distribution. These factors include donor characteristics such as age (Ref. 3), donor infectivity (e.g., with Herpes Simplex Virus) (Ref. 4) length of product storage, storage medium, and shipping distance from the eye bank to the recipient site. In a recent analysis of factors contributing to primary corneal graft failure, Wilhelmus et al. found that "[T]he duration of donor corneal preservation may have a significant effect on endothelial vitality," citing studies that demonstrate endothelial cell loss in chondroitin-supplemented storage media after 7 to 10 days of storage. The authors suggest that, with modern eye bank screening and preservation procedures, a donor corneal storage time greater than 1 week increases the risk of primary failure by more than twofold.

Wilhelmus et al. include in their analysis a summary of selected findings of studies published between 1971 and

1994 reporting primary graft failure for corneal transplants using 4 °C preservation, and using a variety of preservation methods. The rates of primary graft failure ranged from 0.9 to 3.1 percent, and a combined rate of 2.1 percent was estimated across all preservation methods. In their analysis of factors associated with corneal graft failures reported to the EBAA for 1991 to 1993, the findings of Wilhelmus et al. illustrate the importance of documentation of the receipt of supplies and reagents used in tissue processing. The authors found the identical manufacturer's lot number for the preservation medium among 2 media in 34 cases, among 3 media in 36 cases, and among 4 media in 16 cases. Thus, 86 cases (approximately 59 percent of cases) with primary graft failure shared preservation media from the same lots. The lot number was unique in 45 cases (31 percent) and was not recorded in 16 cases (10 percent of cases) involving product failure. These findings also underline the importance of the proposed CGTP-required verification of quality and documentation of each particular lot of processing media used in the manufacture of a uniquely labeled and traceable product.

Primary corneal graft failure typically requires repeat surgery to replace the failed graft. According to the Agency for Health Care Policy Research (AHCPR)[3] (Ref. 5), an estimated 7,443 corneal transplants were performed in 1994, with a mean hospital length of stay (LOS) of 2 days, and a mean total hospital charge equal to $7,530. The estimated rate of primary graft failure resulting from one or more aspects of product collection, processing, or distribution ranges from 0.1 percent (the number of cases officially reported to EBAA for the period 1991 to 1993) to as much as 2.1 percent (combined failure rate reported in the literature, across the range of preservation media currently used in eye tissue processing, cited in Wilhelmus et al.). Based on the AHCPR-reported 1994 volume of corneal transplants, the estimated cases of primary graft failure may range from 7 cases [0.001 × 7,443] to 156 cases [0.021 × 7,443]. The total cost of replacement of a failed corneal graft is estimated to include $454 of physician services, including an office visit to diagnose the graft failure prior to hospitalization[4] (Ref. 6), and initial and follow-up physician visits during patient hospitalization[5] (Ref. 6) for the repeated corneal transplant. It also includes one follow-up physician office visit to assess the outcome of the second transplant. The patient is estimated to further incur at least one week of time lost from work for the doctor visits, hospitalization and recovery of visual function after surgery. The cost of $772 for this patient time loss is estimated based on a 40-hour work week and average hourly compensation of $19.30.[6] Thus, the current cost impact of corneal graft failure may range from $61,292 [7 × ($7,530 + $454 + $772)] to $1,365,936 [156 × ($7,530 + $454 + $772)].

These estimates provide an indication of the potential cost savings from avoided eye tissue product failures, based on corneal transplants. Tissue quality would improve through the institution of multiple good quality practices, including the validation of processing methods, the verification of processes quality control, and improved documentation. Since these events represent only one type of eye tissue product, the potential for benefit across all products in the eye tissue industry may be greater. The estimated benefits of CGTP applied to eye tissue, measured in terms of avoided corneal graft failures, therefore provide a lower-bound estimate of the potential benefits of the proposed rule. Based on just this one type of eye tissue product, the cost of graft failures that may be avoidable through a universal application of good tissue practices ranges from $61,292 per year, with the lower estimated failure rate, to $1,365,936 per year, based on the higher rate of primary graft failure reported in the clinical literature.

2. Conventional Tissue Products

Conventional tissue includes a wide range of products including bone allograft, skin allograft, heart valves, and other products. FDA's survey of the clinical literature indicates that bone, skin and heart valve allograft each presents a different potential for product failure and thus different kinds of benefits from improved quality assurance in product manufacture. The discussion that follows considers three distinct areas of benefit.

a. *Bone allograft products.* An analysis of the incidence, nature, and treatment of infection in bone allograft (Ref. 7) by Lord et al. demonstrates the importance of quality standards and process requirements to prevent tissue contamination. Of the 283 patients in their analysis who had received a massive allograft of bone, infection developed in 33 cases (11.7 percent). The final outcome for those 33 patients was poor compared to the 250 uninfected patients. About 82 percent (27 of the 33) of the infected allograft were considered failures of treatment because amputation or resection of the graft was required to control the infection. Potential sources of contamination cited in the study include donor infection or contamination introduced during processing (estimated to occur in as many as 7 percent of the grafts), in addition to factors such as the duration of the operation, loss of blood, injury to soft tissue, and skin sloughing during the operation. These risk factors highlight the critical need for tissue products that are both sterile and viable.

The importance of processing validation is implied by Hardin (Ref. 8) in a review of banked bone allograft processes. In describing methods for sterilization, Hardin lists ethylene oxide as one of the most commonly used chemicals, but indicates that its effectiveness may nonetheless be questionable, because of reports of graft failures in which residues of ethylene oxide have been blamed, and some experimental evidence indicating toxicity of ethylene oxide in human tissues.

Based on an average rate of 0.057 for bone allograft failure due to contamination (based on an estimated allograft infection rate of 0.07 and an estimated 0.82 failure rate for infected bone allograft), and the assumption that all failures would be treatable through repeat surgery to replace the bone graft, the associated costs could be on the order of $33 million per year [$33,069,348 = 0.057 × 39,000 × ($13,538 + $1,338)]. This is based on a national estimate of 39,000 bone allograft per year[7] (Ref. 9), and an estimated $13,538 per hospitalization

[3] These AHCPR estimates are based on data from the Healthcare Cost and Utilization Project (HCUP–3) National Inpatient Sample. This is a Federal-State-industry partnership to assemble health care data, based on a nationwide inpatient sample of hospital discharge records for 1994, from 20 percent of U.S. community hospitals from 17 States. The HCUP–3 estimated hospital charges do not include physician payments.

[4] An estimated submitted charge of $76 per office visit for ophthalmology care is based on HFCA allowed payments for Medicare beneficiaries in the *Health Care Financing Review* 1997 Statistical Supplement Table 62, adjusted to estimate submitted charges.

[5] An estimated initial hospital visit charge of $214 and subsequent visit charge of $88, based on HFCA allowed payments for Medicare beneficiaries in the *Health Care Financing Review* 1997 Statistical Supplement Table 62, adjusted to estimate submitted charges.

[6] This estimate is based on the 1994 average total compensation of $36,834 adjusted by 2.9 percent annual increase between 1994 and 1997, per the *U.S. Statistical Abstract.* ($36,834 × 1.0293/2080) = $19.3

[7] *Detailed Diagnoses and Procedures, National Hospital Discharge Survey 1995,* Series 13: Data from the National Health Survey, No. 13, November 1997, table 4, p. 131.

for repeat surgery (AHCPR HCUP–3 NIS). Physician costs per hospitalization are estimated to be $1,338 including $135 for each of two specialty physician office visits: one prior to, and one following hospitalization[8] (Ref. 6); and $1,068 for surgeon services while hospitalized, based on HCFA-reported average submitted charges per person served for orthopedic surgery[9] (Ref. 6).

The reported average length of stay for bone surgery is approximately 5 days. The estimated cost of patient time lost assumes that repeat surgery would require at least 1 week of time from work, at an estimated value of $772, based on a 40-hour work week and average hourly compensation of $19.30 (see footnote 6). This yields a total estimated patient time cost of $1,716,156 [0.057 × 39,000 × $772]. The total annual cost of bone allograft failure due to contamination is therefore estimated to be nearly $35 million [$34,785,504 = $33,069,348 + $1,716,156].

If bone allograft failures result in amputation, the direct and indirect costs would be significantly higher. For example, the cost per hospitalization for lower extremity amputation is estimated to be $24,178, based on the AHCPR HCUP–3 data. Moreover, permanent disability following amputation imposes extremely high costs on the patient, and on society.

FDA is uncertain about the extent to which the estimated cost impact will be reduced through CGTP for two reasons. First, some tissue graft failures may result from the transplant procedures rather than the bone allograft manufacture. Second, some facilities may have already developed new bone processing methods that may greatly reduce infection risk. If as much as 75 to 80 percent of the estimated risk is actually attributable to other factors, or has already been addressed through better manufacturing procedures at many facilities, the net benefit from the proposed CGTP rule applied to the remainder of bone tissue processes and facilities would be approximately $8 million [$34,785,504 × 0.23] per year.

b. *Skin allograft products.* Skin allograft represent another type of tissue product that is critically dependent on quality controls to prevent the manufacture and distribution of contaminated or defective products. The clinical literature reports cases of cytomegalovirus (CMV) transmission through skin donor infection (Ref. 10), and HIV contamination from infected donor tissue and subsequent skin tissue handling (Ref. 11). CMV infections are usually not life-threatening in healthy individuals, but present grave risks to the types of patients who typically require skin grafts. In general, patients who have suffered severe burns and require skin grafts are immunosuppressed as a result of their injury and are therefore susceptible to potentially life-threatening CMV infections. These include pneumonitis, retinitis, gastroenteritis, hepatitis, and neurological complications (Ref. 10). Contamination of skin allograft can significantly affect burn patient survival. Because the clinical literature does not provide summary estimates of the risk of contamination of skin allografts, the agency is unable to quantify overall risk. The agency welcomes comment on the rate and severity of skin tissue contamination.

c. *Heart valve allograft.* Heart valve allograft, another conventional tissue product, provide another compelling case for process validation and quality control. Valve tissue contaminants not effectively removed in tissue processing have resulted in serious infections that, at minimum, require valve replacement and that may also result in patient death.

Sources of contamination of a valve allograft include the donor, the environment during harvesting and processing, and the operating room during implantation. Microbial contamination of valve tissue is common at tissue harvesting, with reports of over 50 percent contamination among valves retrieved in open mortuary areas. According to a study by Kuehnert et al. (Ref. 12) common contaminants found before disinfection consist of gastrointestinal and skin flora, including coliforms, viridans group streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus* species. In general, bacterial contamination can be effectively removed through standard disinfection procedures used in most tissue banks. However, tissue that remains contaminated with these pathogens, particularly *Staphylococcus* and *Streptococcus* species, can cause early onset allograft valve endocarditis. In contrast to bacterial contamination, reported rates of fungal contamination are relatively low. However, Kuehnert et al. report that rates vary widely (1.7 percent to 28.0 percent), and that the inclusion of anti-fungal drugs in the tissue disinfection regimen is not effective in eradicating fungal contamination.

Fungal endocarditis is a rare but potentially fatal complication of allograft valve replacement. According to Kuehnert et al., the incidence of fungal endocarditis following surgery for heart valve replacement with allograft is estimated to range from 0.3 percent to 1.4 percent (midpoint estimate of 0.0085). In one reported case, the infected patient needed subsequent surgery to replace the valve and required intravenous amphotericin B for the following 8 weeks. In many cases, treatment is not successful and death results. In one review, cited by Kuehnert et al., over 40 percent of the patients who had acquired fungal endocarditis after valve allograft implantation died within 2 weeks of diagnosis.

In their study, Kuehnert et al. describe the process controls used by AATB-affiliated facilities, including the establishment, validation, and documentation of decontamination protocols. Because these regimens have not been found effective against fungal contamination, AATB-affiliated facilities routinely discard tissue with documented fungal contamination. However, according to Kuehnert et al., the supplier of over 85 percent of all heart valve allograft does not follow AATB standards, but instead follows a decontamination protocol that is reported to be proprietary. This protocol apparently includes efforts to disinfect rather than discard tissue with fungal contamination. However, efforts to eradicate fungal contamination identified in processing can be unsuccessful, and in this case, a false-negative culture following processing resulted in the tissue being distributed for patient use.

The proposed rule would require that all facilities validate the effectiveness of each step in processing, and would require that contaminated tissue that cannot be effectively disinfected be discarded or otherwise removed from processing for distribution. Based on the rates of infection and mortality risk reported by Kuehnert et al., and a total of 61,000 heart valve allografts reported per year by the National Hospital Discharge Survey (Ref. 13), there may be an estimated 519 cases per year [0.0085 × 61,000] of heart valve contamination causing fungal endocarditis. These contaminated valves may further cause an estimated 207 deaths per year [0.0085 x 0.40 x 61,000]. Changes in processing based on the proposed CGTP requirements would help to avoid these deaths. Substantial health care cost

[8] An estimated cost of $135 per service based on average submitted charges per service for "All Other Physician" specialty groups is used to estimate specialist office visit charges. This cost per service is reported in the *Health Care Financing Review* 1997 Statistical Supplement Table 59.

[9] See *Health Care Financing Review* 1997 Statistical Supplement Table 59, Submitted Charges, for Orthopedic Surgery.

savings could also be achieved through improved processing controls. Based on an average cost of $63,096 per hospitalization for implantation of a heart valve allograft (Ref. 5), and estimated physician charges of $6,796 per case, including repeat surgery and patient care during the average 13-day hospital stay. If the CGTP requirements avoided 80 percent of these valve infections, this might result in health care cost savings of up to $29 million [0.8 x 519 x $63,096 + $6,796)].

3. Stem Cell Products

According to the National Center for Health Statistics National Hospital Discharge Survey, approximately 8,000 stem cell transplant procedures were performed in 1994. Based on the AHCPR HCUP–3 NIS data for 1994 (Ref. 5), the average length of hospital stay for bone marrow transplant procedures was 35 days, with an average cost per stay of $168,573.

Promising outcomes from use of peripheral blood stem cells (PBSC) and cord blood-derived stem cells (CBSC) in lieu of bone marrow have resulted in increased collection and use of these products in stem cell transplants. For example, recent studies have respectively reported use of PBSC (rather than bone marrow) in 54 percent (Ref. 14) and 62 percent (Ref. 15) of cases. However, studies of stem cell products indicate that products manufactured by this industry can become contaminated during collection and processing. Moreover, the therapy-induced immunosuppression of the oncology patients who receive these products places them at particular risk for serious infection and subsequent mortality. Manufacturing methods conforming to good tissue practice are necessary to prevent this threat to the safety and effectiveness of stem cell therapies. For example, earlier investigations of PBSC reported that the large quantity of blood that must be processed to obtain adequate numbers of stem cells resulted in large volumes of cryopreserved cells received by patients. This process posed the risk of increased toxicity, because of the amount of dimethyl sulfoxide used for cryopreservation (Ref. 16).

Another quality concern with PBSC involves the maintenance of sterile integrity of the apheresis catheter and component throughout the period of leukopheresis, cryopreservation, thawing, and transfusion (Espinosa et al., 1996). Webb et al. (Ref. 14) reported a 2.41 percent rate of bacterial contamination in PBSC products, and a 13.7 percent rate of infection of patients receiving contaminated products.

Although the bacteremia-induced fever and other clinical sequelae are considered reversible, infections present more serious risks in stem cell recipients than for the general population. Survival rates for hematopoietic stem cell transplantation are significantly reduced for patients that become critically ill. In a study of survival rates among stem cell recipients admitted to an intensive care unit, Price et al. (Ref. 15) found that patients with probable infection had a significantly higher death rate (57 percent) compared to patients with no probable infection (13 percent). Multiple regression analyses by Price et al., to predict probability of death controlling for other risk factors such as patient intubation, type of transplant, source of stem cells, human leukocyte antigen compatibility, type of malignancy and patient age, also found infection to be a significant predictor of mortality.

An estimated 15 patients per year could suffer infection following receipt of contaminated PBSC, based on the reported rates of 2.4 percent of patients receiving contaminated PBSC, 13.7 percent of those patients subsequently developing infection, and 8,000 stem cell transplants reported for 1994, and assuming that 58 percent of stem cell transplants (the average of the two reported rates of PBSC transplant cited above) involve PBSC. Costs of treating patients who become infected after receiving contaminated stem cell product are based on an average AHCPR-reported hospital charge[10] (Ref. 5) of $17,981 per 9-day patient stay for treatment of bacterial infection. Estimated health care costs also include physician costs of $918 assuming one initial hospital visit, and daily follow-up visits during the patient stay[11] (Ref. 6). Patient time loss during the hospitalization is valued at $1,387, based on estimated hourly compensation of $19.30 (see footnote 4) and a 9-day hospital stay. Thus, the total annual cost impact of patient infection following transplant of contaminated PBSC products is estimated to be $304,290 [15 x ($17,981 + $918 + $1,387)].

In addition to avoided health care costs, eliminating the risk of contaminated products could yield a potential of seven avoided stem cell patient deaths per year, due to infection. This number reflects the excess mortality risk reported for stem cell recipients with infection versus those without infection. It is based on the following: (8,000 transplant procedures per year) x (58 percent of procedures with PBSC) x (2.41 percent PBSC patients receiving contaminated product) x (13.7 percent patients receiving contaminated product develop infection) x (57 percent to 13 percent) excess rate of death for stem cell recipients given presence of infection.

As bacterial contamination has also been documented in a study of cord blood processing, the proposed CGTP requirements for staff training and process validation would support similar risk reduction efforts across CBSC facilities. For example, a study by Kogler et al. (Ref. 17) found that during the initial 6 months of an unrelated CB collection program, the median bacterial contamination rate was 18 percent. After extensive training in sterile procedures for the staff who collect cord blood, the contamination rate was reduced to 1 percent.

4. Reproductive Tissue Products

Most aspects of cellular and tissue product manufacturing in the reproductive tissue industry would become newly regulated under the proposed CGTP rule. The affected establishments within this industry include sperm banks and ART facilities. Reports of the sensitivity of product quality to variations in tissue collection, technician skill, processing methods, environmental conditions, and other factors (Ref. 22), indicate that the risk of communicable disease transmission would be reduced by improving the proposed overall product quality, and economic benefits would be seen through improved patient outcomes from facility compliance with the proposed CGTP requirements.

The tissue used in commercial sperm banks is washed, processed, and cryopreserved donor sperm used for therapeutic donor insemination (TDI). The sperm are obtained generally from paid donors who have been screened and tested for infectious disease and certain genetic disease risks.

The tissues used in ART facilities include fresh or cryopreserved oocytes, sperm, zygotes, and embryos. The handling of tissues include but are not limited to: Retrieval of oocytes from a

[10] Based on AHCPR HCUP–3 National Inpatient Survey for 1994 hospital charges by principal diagnosis, "bacterial infection, unspecified site" ($17,891), *http://www.ahcpr.gov/data/94dcchpr.htm*. 1998.

[11] Physician charges are based on estimates of physician submitted charges using data reported in the Health Care Financing Review Statistical Supplement, 1997, table 62. Initial inpatient visit charge is estimated to be $214, and daily follow-up visits in the hospital are estimated to be $88 per visit. Thus total physician charges for care during the 9-day hospital stay are estimated to be $918.

female, collection of sperm from a male, in vitro fertilization (IVF), cryopreservation of fertilized oocytes not transferred in the same treatment cycle, and thawing of frozen fertilized oocytes. The success of in vitro fertilization, measured as the number of deliveries per IVF cycle, has gradually increased over the past decade or so, from 11 percent in 1985 to 18 percent in 1994 (Ref. 18). More recently, the Centers for Disease Control and Prevention (CDC) have reported average live birth pregnancy rates for ART clinics to be as high as 19.6 percent per cycle in 1995 and 22.6 percent per cycle in 1996 (Refs. 19 and 20).

Despite the increasing effectiveness of infertility treatment through ART, problems can occur in tissue processing. Adverse outcomes owing to problems with product quality can result from contamination that produces infection (e.g., HIV transmission) in the infertility patient (Ref. 21). Problems with ART facility processing of sperm or oocytes can also lead to reduced rates of fertilization, and unsuccessful IVF attempts, which would ultimately increase the number of transfer attempts. Each additional transfer attempt increases the risk of communicable disease with each attempt.

Where quality problems in tissue processing result in reduced embryo quality and lower probability of pregnancy, the patient, on average, needs to undergo more cycles of IVF to achieve a pregnancy that produces a live birth. The estimated patient cost per cycle ranges from $8,000 to $10,000 (Refs. 24 to 26).

The number of Americans who would potentially benefit from improved reproductive tissue processing is substantial. According to the 1995 National Survey of Family Growth (NSFG), (Ref. 28) 15.4 percent of American women 15 to 44 years of age, approximately 9.3 million women, have reported receiving infertility services. Approximately 600,000 women report receiving ART's, defined in NSFG to include artificial insemination and IVF services. The number of ART procedures annually has been increasing in recent years. According to the CDC (Ref. 29) a total of over 64,000 cycles of ART were performed by U.S. facilities in 1996, compared to approximately 60,000 cycles in 1995. The proposed CGTP rule, therefore, has the potential to benefit thousands of infertile couples.

Processes that affect product quality. Recent clinical literature reports a number of factors in the manufacturing process that could affect tissue quality. These factors include technician skill, equipment accuracy and reliability, methods used in laboratory processing, and environmental controls affecting product quality. Following process validation and quality controls that would be required under the proposed rule is expected to substantially reduce or eliminate detrimental variations, and thereby improve product quality.

Sperm processing occurs in both commercial sperm banks and ART facilities. Commercial sperm banks generally screen, wash, and cryopreserve donor sperm. ART facilities typically include an andrology laboratory that performs semen analysis and conducts IVF. Variations in methods and technician skills at various stages of sperm processing have been associated with variations in quality. Poor sperm quality increases the probability that additional tissue transfer procedures will be necessary. For example, in a study conducted to establish quality controls in semen analysis, Yeung et al. found that the subjective thresholds for judging sperm motility (a key measure of sperm function for diagnosis and treatment) differed for each technician performing the analysis (Ref. 30). The establishment of values for threshold velocities, and standards for technician training were identified as methods to improve consistency in technician assessments.

A study by Mahmoud et al. (Ref. 31) compared 10 different methods for estimation of sperm concentration (another key indicator of sperm quality) and reported substantial differences in the accuracy of laboratory assessments, depending upon the type of pipette and the method used. They found that although a few devices and methods produced accurate, low-variability estimates, others had a tendency to overestimate or to underestimate sperm concentration. These findings strongly support the need for equipment calibration and laboratory method validation.

In addition to processing steps related to the sperm quantity and quality, sperm processing for IVF typically requires that sperm be purified, removing semen fluid, cellular debris, white blood cells, and other contaminants that may interfere with fertilization. Many sperm separation methods have been developed and are in use in ART programs, including basic sperm washing, swim-down and swim-up techniques, refrigeration/heparin techniques, separation with Sephadex and Ficoll columns, separation with glass wool and Percoll gradient centrifugation (Refs. 32 to 34). No single method has become the standard, although some approaches may be more effective than others in preserving functional integrity. For example, when King et al. (Ref. 35) compared the effect of different antibiotics used in sperm washing, they found that some agents produced severe adverse effects on sperm motility and actually decreased sperm fertilizing capacity. The importance of product quality in this step of processing offers another example of the value of process validation in ensuring sperm product viability and thus successful fertility treatment for patients.

Environmental controls present another area with a demonstrated need for quality control in reproductive tissue processing. Environmental contamination may come from many sources, including the air, water or laboratory supplies. A study of laboratory air quality in ART facilities by Cohen et al. (Ref. 36) found that over 300 volatile organic compounds were detectable in spite of the use of centralized high efficiency particulate air (HEPA) filtration, generic but centralized carbon and pre-filtration, and numerous ionization units placed at strategic points in the laboratory. Potential sources of contaminants included vehicle and industrial emissions in outside air, use of plastics and disposable plasticware in the laboratory, equipment (e.g., freon leakage from refrigeration units), cleaning agents and equipment lubricants, and air flows from activities in adjacent areas of the building.

A more detailed study of these factors by Cohen et al. was prompted in part by the sudden and significant declines in clinical pregnancy and implantation rates that occurred at two points in time at an ART facility. In those instances, the pregnancy rate had declined by about 50 percent and subsequent implantation rates also declined. Their investigation revealed that, in the first instance of decline, a fumigation with pesticides had taken place in areas of the building adjacent to the ART facility, without notification given to the ART facility. The second episode of sudden decline corresponded to the installation of a redesigned air filter in the facility. Further air sampling also revealed that chemical contaminants produced in another area of the building, which was used as an outpatient surgery center and was not part of the ART clinic, could be detected in the embryo laboratory when more sensitive monitoring equipment was used. Cohen et al. proposed various measures to counter these potential sources of chemical air contamination in both the laboratory and the embryo

incubators. Laboratories without adequate environmental monitoring and controls would not be able to detect such degradations in air quality.

An earlier study of mouse embryos by Francis et al. reported that some brands of nonpowdered surgical gloves appear to be embryotoxic (Ref. 37). Temperature fluctuations during cell culture, and to a lesser extent, the time between retrieval and transfer, may also affect tissue quality and thus increase the probability of additional transfer attempts (Ref. 39).

The lack of experience and training of laboratory personnel also could increase the need for additional transfer attempts due to poor tissue quality. One study found that new embryologists needed several months to gain the experience to consistently predict nuclear maturity from cumulus-coronal morphology. Moreover, even when a stable prediction rate was reached, it rarely exceeded 72 percent accuracy (Ref. 40). Yet consistent assessments of product quality and transfer of high quality embryos to the patient are critical to increasing the overall success of IVF treatment and to minimizing transfer attempts.

Although there has been some Federal and some private sector standard setting and oversight in the reproductive tissue industry, existing standards do not provide the level of quality management and process quality assurance that would be required under the proposed CGTP rule for all tissue establishments. A voluntary accreditation program jointly offered by the CAP and the ASRM has been available to ART laboratories since 1992 (Refs. 41 and 42), and the number of facilities seeking accreditation has been increasing in recent years. The problems with product processing cited in recent clinical literature, however, suggest that although there is increasing interest in quality assurance, there are still substantial gains that could be made in tissue facilities, by implementing the proposed CGTP rule.

In addition to the benefits that would accrue directly from implementation of this proposed rule, individuals may reap ancillary benefits that could arise indirectly from the rule. Although the proposed rule would provide a direct benefit from the decreased risk of communicable disease transmission, the public, particularly couples seeking assistance in beginning a pregnancy, could receive an indirect economic benefit. Such ancillary economic benefit, although not certain, would be seen as an increase in ART facility success rates and a decrease in health costs associated with a reduction in the number of IVF attempts per live birth.

FDA cannot predict the precise impact from implementation of the proposed CGTP rule. To obtain an estimate of benefits and to capture a level of uncertainty, this analysis considers three potential scenarios and presents the results a range of possible outcomes. In general, it is assumed that the rule will affect the facilities with the lowest success rates and that these facilities would improve to some minimal level of performance from the implementation of good practices. In one scenario, benefits are assumed to be limited to the worst-performing quarter of all facilities. These facilities would improve to the level of the facility just better than the bottom one-fourth. In another scenario, the half of all facilities with the lowest success rates would improve to where they would be as good as the median facility. In a third scenario, implementation of the rule would not change ART facility success rates.

The scenarios consider only the cycles of treatment for younger women (age less than 35) for whom patient age is not likely to be a confounding factor affecting oocyte quality. Of the 22,811 fresh nondonor cycles of treatment for these patients at the 300 ART facilities reporting data for 1996, the average success rate was 28.65 live births per 100 cycles, and the median live birth pregnancy rate was 26.3 percent per cycle.

Scenario 1 assumes that the facilities currently achieving the lowest success rates (i.e., the lowest quartile of success rates reported for ART establishments) are able to increase their average success rate to the rate corresponding to the 25th percentile rate. This would represent a first step and as technology and techniques continue to improve, so would success rates. In the 1996 report, the 25th percentile rate was 19.7 live births per 100 cycles. FDA finds that raising the bottom quartile of 75 facilities, to 19.7 live births per 100 cycles, would reduce the IVF attempts from a reported 4,756 to an estimated 3,591 treatment cycles. This improvement would decrease transfer attempts and yield an estimated savings of $10.5 million for patients and other payers, based on an estimated average cost of $9,000 per cycle, and an estimated 1,165 avoided cycles [4,756 − 3,591].

Scenario 2 assumes that facilities in the lower half of the industry distribution are able to bring their success rates up to the median rate of 26.3 live births per 100 cycles. The increased success rate is assumed to be achieved through improvement in staff training and skill, processing validation, and quality control throughout the facility in accordance with the proposed CGTP rule. Under this scenario, the affected 150 facilities would reduce the number of IVF attempts from a reported 10,414 cycles to an estimated 7,662 treatment cycles, to achieve the same number of successful treatments. This would yield an estimated cost savings of $24.8 million for patients and other payers. This is based on an estimated 2,752 avoided cycles of treatment [10,414 − 7,662] and assumed average cost of $9,000 per cycle of IVF treatment.

At the other end of the spectrum, Scenario 3 provides for the possibility that this proposed rule would have no effect on success rates at ART facilities or the number of IVF attempts per live birth. In such a case, there would be no additional economic benefit beyond the benefits previously discussed, including an anticipated decrease in communicable disease transmission.

Couples seeking infertility care incur an indirect cost of time lost (e.g., work time) while undergoing treatment. Using an average hourly wage of $19.30[12] and assuming 6 hours of time (e.g., 4 hours for the female and 2 hours for the male patient) per couple per cycle of IVF treatment, the estimated value of the lost time would be as follows. Under Scenario 1, the estimated 1,665 avoided treatment cycles would yield a time gain valued at $192,807 [1,665 × $19.30 × 6]. Under Scenario 2, the 2,752 potentially avoided treatment cycles would yield a time gain valued at $318,682 [2,752 × $19.30 × 6]. Under Scenario 3, there would be no avoided treatment cycles and, thus, no quantifiable benefits.

C. Summary of Potential Benefits Resulting From Avoided Quality Problems in Processing of Cellular and Tissue Based Products

This analysis of benefits of the proposed CGTP rule has considered its impact on major sectors of the tissue industry by focusing on product quality problems cited in the literature. This review suggests that industry standards are not applied uniformly resulting in uneven product quality.

Table 10 provides a summary of the particular products and problems identified in the agency's survey of literature. FDA estimated the potential benefits of avoiding quality problems based on reported risks and national

[12] Estimated hourly compensation of $19.30 is based on the 1994 average total compensation of $36,834, adjusted by 2.9 percent annual increase reported in the 1997 *U.S. Statistical Abstract*.

data-based estimates of the number of patients undergoing related procedures. Depending on the particular industry sector, the potential quantified benefits from reduced health care costs are estimated to range from approximately $61,000 per year, to approximately $33.5 million per year. The total estimated potential quantified benefits range from a total of $41.9 million to $68.0 million. The actual level of benefits that would be realized through wide application of CGTP is uncertain, however, as the agency's projections are sensitive to numerous assumptions that appear plausible, but remain to be tested.

TABLE 10.—SUMMARY OF POTENTIAL BENEFITS OF PROPOSED CURRENT GOOD TISSUE PRACTICE BASED ON TISSUE PROBLEMS CITED IN REVIEWED LITERATURE

Tissue Industry Sector	Tissue(s) Considered	Avoided Problems with Tissue	Avoided Treatment or Outcome	Potential Cost Savings/ Year
Eye Tissue	corneal graft	graft failure	repeat surgery; increased graft attempts	$61,000 to $1.4 million
Conventional Tissue	bone allograft	bone infection; graft failure	repeat surgery/amputation; increased graft attempts	$8 million
Conventional Tissue	heart valve allograft	fungal endocarditis	repeat surgery/patient death; increased transplant attempts	$29.6 million 176 excess deaths
Peripheral Blood and Cord Blood Stem Cells	stem cell transplant	infection in cancer patients	hospitalization/patient death	$304,000 7 excess deaths
Reproductive Tissue	sperm, oocytes, zygotes, embryos	IVF[1] failure	additional IVF treatment cycles	$0 to 24.8 million
Total Potential Cost Savings/Year				$41.9 to $68.0 million

[1] In vitro fertilization

Uncertainties affecting the true level of benefit include: The actual extent of current CGTP compliance in each of the affected industries, the lack of more complete information about the incidence and severity of problems from processing of tissue products, the net impact of those quality problems on patient outcomes, and the size of the affected patient population. Because of the limits of available data, the foregoing analysis has focused on a limited set of tissue products. It is not certain how well these data represent the most critical areas or actual scale of risks in the tissue industry. For some products, such as demineralized bone, the industry has achieved important advances in processing that have improved the safety and effectiveness of its products. Thus, the analysis of benefits based on problem reports from several years ago may overstate the potential for improvements in the current best industry practice. In other cases, the publication of the recent problem reports suggests that deficiencies still exist within current practices. These areas present important opportunities to avoid unnecessary patient risks and health care costs.

D. Small Entity Impacts

The Regulatory Flexibility Act (RFA) requires agencies to determine whether a proposed rule may have a significant effect on a substantial number of small entities. Tissue and blood banks are classified in North American Industry Classification System (NAICS) 621991. In this industry category, any firm with annual revenues less than $5.0 million is considered small by the U.S. Small Business Administration. In every sector of the cell and tissue product industry, the majority of establishments are estimated to be classified as small entities. However, because of the high level of current compliance with industry standards, the increase in costs is expected to be limited primarily to facilities that do not comply with industry standards. To measure the impact of CGTP on small businesses, FDA calculated the ratio of industry compliance costs to industry revenues, assuming that all facilities incurred the same cost. The small entity impacts estimated below focus on the facilities that will be newly compliant under the proposed CGTP, and thus will experience the highest potential new costs. In addition, although current quality management practices at non-accredited or less-than-fully compliant facilities may vary, and not every facility will incur every new cost estimated in table 2, the analysis that follows considers a high-cost scenario where every estimated cost is incurred, in order to produce a conservative estimate of the potential impact on small entities. While some firms may have lower than average revenues, making them potentially more sensitive to cost increases, FDA does not know the distribution of firms by revenues. FDA welcomes comments on this issue.

Within the eye banking industry, experts estimate that virtually all facilities would be classified as small, and believe all are to be compliant with the industry EBAA standards. The average annual revenue per eye bank is estimated at $1.2 million (Ref. 44). If an eye bank were to incur every new cost estimated for facilities in that industry, the total cost impact, including total one-time costs and the yearly cost, would be $36,738, which represents an estimated 3 percent (0.03) of estimated annual revenues. Average annualized compliance costs per eye bank are estimated to be $10,717, or 0.89 percent of annual revenue per firm.

In the conventional tissue industry, an estimated 75 to 80 percent of the total of 110 facilities would be classified as small entities. Industry experts also estimate that 75 to 80 percent of those facilities currently comply with the AATB standards, which generally meet or exceed the requirements of the proposed CGTP rule. Based on the assumed levels of increased effort and costs shown in table 2, the remaining 23 percent of small facilities that do not comply with AATB standards would incur up to $62,662 in total new costs, including both the total one-time cost and the yearly cost, assuming that every potential area of new quality management effort would be needed at every one of these facilities. The average annual revenue per small conventional tissue bank is estimated at $1.2 million (Ref. 44). The estimated total new costs would represent approximately 5 percent of this annual revenue figure. The average annualized compliance cost for a small conventional tissue bank is estimated to be $10,310, representing 0.86 percent of firm revenues.

The agency anticipates that all stem cell facilities would be classified as small entities, and estimates that these establishments have annual revenue averaging $1.2 million (Ref. 44). Establishments that comply with the current FAHCT or AABB standards would incur some additional costs. If each of these facilities were to incur new costs for every provision identified in table 2, the total cost per facility, including total one-time and yearly costs, would be approximately $20,270. This figure represents approximately 2 percent of estimated annual revenues. Stem cell facilities that do not currently comply with AABB or FAHCT standards would incur greater costs, as shown in table 2. If each of these facilities were assumed to incur every new cost identified in the cost analysis, the total one-time cost plus annual cost would be approximately $79,337. This figure is equal to approximately 7 percent of estimated annual revenues. The average annualized compliance costs incurred by stem cell facilities would similarly vary depending on current facility practices and compliance with AABB or FAHCT standards. If a facility is currently compliant with these industry standards, the average annualized cost of compliance with the proposed rule is estimated to be about $7,407, representing 0.62 percent of the yearly revenue of these firms. However, if a facility is not currently compliant with the requirements of the current industry standards, a greater level of new effort would be required for quality assurance and quality management. The average annualized cost per facility is estimated to be $40,721, which would represent 3.39 percent of an average annual revenue of $1.2 million.

Consultants estimate that approximately two-thirds of all ART facilities (approximately 200) would be classified as small entities, and have average annual revenues of $2.5 million. Based on the project levels of compliance with various provisions of CGTP, as described in the cost analysis, if a facility were to incur every potential new cost, as shown in table 2, the total one-time plus annual cost to the facility would be $83,302. This total would represent approximately 3 percent of average annual revenues. The average annualized compliance cost per facility is estimated to be $11,342, representing approximately 0.45 percent of annual revenues.

According to recent estimates by a sperm banking industry expert, approximately 100,000 TDI units are produced each year from collected and processed sperm donations. An estimated 95 percent of that total production is handled by the largest 20 facilities. Nineteen of the largest 20 facilities are estimated to have average annual revenues of approximately $2 million, and only 1 of the 20 is estimated to have revenues greater than $5 million per year. The remaining 5 percent of industry production, or 5,000 TDI units, are processed by very small banks described by an industry expert as typically functioning within a physician office practice (e.g., that of an obstetrician (ob) or a gynecologist (gyn)). The sperm banking in these facilities is generally offered as an additional service to patients receiving fertility treatment, and is not the primary line of business of these establishments. The annual revenue for these individual physician practices is estimated to be $252,000 per year, based on the mean physician income of $215,000 after expenses and before taxes for the ob/gyn specialty category, reported in the 1992 American Medical Association (AMA) survey (Ref. 45), adjusted to 1998 assuming an average annual wage inflation of 2.7 percent, based on yearly rates reported by the Bureau of Labor Statistics. Thus the majority of sperm banks would be considered small entities.

If each of the small sperm banks were to incur every potential new cost of compliance with the proposed CGTP rule, as shown in table 2, the total one-time cost plus annual cost would equal $83,302, which would be approximately 4 percent of the $2 million in annual revenues for the "larger" small facilities. The average annualized cost to these banks is estimated to be $11,007, representing approximately 0.55 percent of annual revenues. Although these cost figures would account for a much larger percentage of individual physician practice income, the sperm banking provided by these establishments is considered to represent a small and generally nonessential part of their business. For the smallest banks, the estimated 5,000 TDI units supplied by the estimated 90 facilities translates to an average volume of 55 units per facility per year. With an estimated price of $95 to $145 per TDI unit (Ref. 46) and an estimated profit of 15 percent, the banks would realize a net income of $12.40 to $19.00 per unit, or average net income of $682 to $1,045 for 55 units. This income would represent only 0.3 percent (0.0027) to 0.4 percent (0.0041) of the estimated $252,000 in annual net income for the ob/gyn physician practice. Thus, it seems likely that physician practices that currently operate small-scale sperm banking may prefer to discontinue banking, and refer their patients to a commercial bank for this service.

In summary, the majority of facilities within each sector of the tissue industry are expected to qualify as small entities. The actual cost impact on each facility is uncertain because of the limited information available to describe the current practices and compliance with industry standards at each of these facilities and within each distinct industry sector. Based on the limited available data and expert opinions, the agency estimates impacts that would result in an average annualized cost per facility ranging from $ 7,000 to $11,000 for facilities that currently comply with an industry standard, to over $40,000 in average annualized costs for facilities that do not currently comply with most industry quality standards. These annualized costs represent 0.45 to 3.39 percent of the estimated total average annual revenues.

The agency is uncertain about the accuracy of these estimates, however, because of the lack of good data on revenues for these facilities. Because of the importance of this information in accurately assessing the impact on small entities, the agency requests that industry provide detailed comment on the percentage of facilities that qualify as small entities in the eye tissue, conventional tissue, stem cell, and reproductive tissue industries; the percentage of those facilities that fully comply with current industry standards; and the specific areas where industry anticipates substantial differences between current manufacturing practices and the quality assurance elements specified under the proposed rule. For those areas of identified difference, the agency further requests estimates of the resources and costs that will be required for facility compliance.

Although the proposed rule would impose some costs on small entities involved in the manufacture of cellular and tissue-based products, the agency believes that the proposed approach represents an effective means of protecting patient safety and public health in the manufacture of human cellular and tissue-based products. The less burdensome alternative to the proposed approach, i.e., continue with the use of trade organizational standards by industry, involve fewer requirements for small entities (the vast majority of facilities in this industry), but fail to provide fundamental aspects of product safety. Reliance on trade organization voluntary standards for good tissue practice, rather than establishing a regulatory requirement, would not ensure uniform or consistent

compliance and would preclude the agency's ability to effectively monitor tissue products to ensure public health and safety. While each trade organization varies in their standards or guidelines, regulatory requirements for good tissue practice would help ensure consistency among manufacturers. FDA finds that this proposed rulemaking would enhance both public health and public confidence in the safety and quality of cellular and tissue-based products, while imposing only a minimum burden on the affected industry sectors.

IX. References

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

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X. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 350193520). A description of these provisions is shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Reporting and Recordkeeping Requirements in Current Good Tissue Practice.

Description: Under the authority of section 361 of the PHS Act, FDA is proposing new regulations to require manufacturers of human cellular and tissue-based products to follow CGTP, which would include information collection provisions such as the establishment and maintenance of SOP's, recordkeeping, reporting, and labeling of the products. The CGTP information collection provisions would provide: (1) additional measures for preventing the introduction, transmission, or spread of communicable diseases; (2) step-by-step consistency in the manufacturing of the product; (3) necessary information to FDA for the purpose of protecting public health and safety; (4) accountability in the manufacturing of cellular and tissue-based products; (5) information for meaningful FDA inspections; (6) information facilitating the tracking of a product back to its original source or to a recipient; (7) information to FDA of any adverse reaction; and (8) information that would aid in the investigation of any introduction, transmission, or spread of a communicable disease.

Table 11 lists provisions that would require reporting or disclosure of information to third parties, the Federal government, or the public. Section 1271.155(a) would require the submission of a request for FDA approval of an exemption or an alternative from any requirement in subpart C or D of part 1271 of the proposed rule. When documentation on the determination of donor suitability is translated into English, § 1271.270(c) would require a statement of authenticity by the translator. Section 1271.290(c) would require a unique identifier be affixed to each cellular or tissue-based product to relate the product to the donor and all records pertaining to the product. Whenever an establishment initially distributes product to a consignee, § 1271.290(f) would require the establishment to inform the consignee, in writing, of the product tracking requirements and the methods the establishment uses to fulfill the requirements. Establishments described in proposed § 1271.10 would be required under proposed § 1271.350(a) and (b) to report to the agency any adverse reaction or any error or accident that may reasonably be expected to lead to a reportable adverse reaction as defined in proposed § 1271.3(ee). Section 1271.370(a)(2) and (a)(3) would require establishments to include specific information on the product label and package insert.

Table 12 lists recordkeeping provisions under the proposed rule, establishments would be required to prepare and maintain written SOP's for all significant steps performed in the manufacturing and tracking of human cellular and tissue-based products. As calculated in table 12, the preparation of the SOP's would result in a one-time impact on establishments rather than the year to year maintenance of the SOP's because, once composed, SOP's would only be reviewed annually and updated as necessary.

The SOP provisions proposed under part 1271 in the combined maintenance estimate include: (1) § 1271.160(b)(2) (receiving, investigation, evaluating, and documenting information received from other sources); (2) § 1271.160(f) (quality program); (3) § 1271.180 (all significant steps performed in the manufacture of human cellular and tissue-based products); (4) § 1271.190(c)(3) (facility cleaning and sanitization); (5) § 1271.195(a) (control and monitoring of environmental conditions); (6) § 1271.200(b) (cleaning, sanitizing, and maintenance of equipment); (7) § 1271.200(c) (calibration of equipment); (8) § 1271.210(a) (receipt and verification of supplies and reagents); (9) § 1271.210(b) (validation and/or verification of in-house reagents); (10) § 1271.220(b) (use and removal of processing material); (11) § 1271.220(d) (control of in-process product); (12) § 1271.225(a) (verification or validation of changes to a process); (13) § 1271.230(d) (maintenance and control of validated processes); (14) § 1271.250 (labeling of human cellular and tissue-based products); (15) § 1271.265(a) to (c) (receipt, acceptance or rejection, distribution, and destruction or other disposition of human cellular or tissue-based products); (16) § 1271.265(f) (suitable for return to inventory); (17) § 1271.270(b) (records management system); (18) § 1271.290(b) (method of product tracking); and, (19) § 1271.320(a) (review, evaluation, and documentation of all complaints).

Proposed part 1271 would require the following additional recordkeeping provisions listed under table 12. Section 1271.155(f) would require an establishment operating under the terms

of an exemption or alternative to maintain documentation of the terms and date of FDA approval. Section 1271.160(b)(3) would require documentation of corrective actions taken as a result of an audit of the quality program. Section 1271.160(b)(7) would require documentation of all product deviations in manufacturing cellular or tissue-based products. Section 1271.160(d)(3) would require documentation of the results of all audits and reaudits of the quality program. Section 1271.160(e) would require documentation of computer validation activities and results when computers are used as part of the quality program, as part of manufacturing, or for maintaining data or records. Section 1271.170(d) would require the maintenance of records of education, experience, training, and retraining of all personnel. Section 1271.190(c)(4) would require documentation of all significant facility cleaning and sanitation. Section 1271.195(c) would require documentation of environmental control and monitoring activities. Section 1271.200(e) would require documentation of all equipment maintenance, cleaning, sanitizing, calibration, and other activities. Section 1271.210(c) would require documentation of the receipt, verification, and use of each supply or reagent. Section 1271.220(b) and (d) would require documentation of the adequate removal of processing material and the verification activities for in-process product. Section 1271.225(b) would require documentation of all changes to established processes, including rationale and the date of implementation. Section 1271.230(a) would require documentation of validation activities when the results of a process cannot be fully verified by subsequent inspection and tests. Section 1271.230(b) would require documentation of the validation of any process-related claim. Section 1271.230(e) would require documentation of the review and evaluation of a process and revalidation of the process, if necessary, when any changes to or deviations from a validated process occur. Section 1271.260(b)(3) and (d) would require documentation of the storage temperature of human cellular and tissue-based products and any corrective action taken when acceptable storage conditions are not met. Section 1271.265(a) and (b) would require documentation of the receipt, acceptance or rejection, distribution, and destruction or other disposition of a human cellular or tissue-based product. Section 1271.270(a) and (c) would require documentation of each significant step in manufacturing required in subparts C and D of part 1271, the results and interpretation of all testing and screening for relevant communicable disease agents and diseases, and the determination of donor suitability.

Section 1271.180 would require the retention of obsolete procedures for 10 years. Section 1271.270(e) would require the retention of all records for a period of 10 years after their creation. Records pertaining to a particular human cellular or tissue-based product would be required to be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product. If the date of implantation, transplantation, infusion, or transfer is not known, then records would be required to be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. This retention time is necessary because certain cellular and tissue-based products have long storage periods. In addition, advances in medical technology have created opportunities for diagnosis and therapy for up to 10 years after recipient exposure to a donor later determined to be at risk for communicable disease agents or diseases.

Section 1271.270(f) would require documentation of any contract, agreement, or other arrangement with another establishment under which any step in the manufacturing process is performed by the other establishment. Section 1271.290(e) would require documentation of the disposition of each of its human cellular or tissue-based product as part of its tracking method. Section 1271.290(f) would require an establishment to document that a consignee agreed to participate in its tracking method and will take all necessary steps to ensure compliance with the requirements of the regulation. Section 1271.320(b) would require an establishment to maintain a record of each complaint that it receives, including a review and evaluation. Section 1271.350(c) would require the documentation of adverse reaction reports, errors and accidents in manufacturing that may lead to product deviation reports, and the investigation of these reports.

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

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

TABLE 11.—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.155(a)	1,065	1	1,065	3	3,195
1271.270(c)	1,065	1	1,065	1	1,065
1271.290(c)	791	250	198,215	0.08	15,857
1271.290(f)	1,065	1	1,065	1	1,065
1271.350(a)	1,065	6	6,390	0.5	3,195
1271.350(b)	1,065	2	2,130	0.5	1,065
1271.370(a)(2) and (a)(3)	633	207	131,005	0.25	32,751
Total					58,193

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

TABLE 12.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
One-time Burden (Creation of SOP's [2])	1,065	9	9,585	16	153,360
One-time Burden (Review of existing SOP's for compliance)	1,065	19	20,235	5	101,175